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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 13 1954

THE LIVER AS A SITE AND SOURCE OF CANCER*

BY

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The subject of my lecture may well seem to you to be ill chosen, since primary cancer of the liver is uncommon in this country and secondary carcinoma presents few problems to the clinician because of its ill omen as the harbinger of death. My excuse lies in the belief that both the natural history and the experimental study of liver cancer afford precise information from which we may derive hints about the cancerous state and thereby acquire some guidance in the planning of future work.

With the idea of orientating myself to the pathological aspects of the discussion I asked two of my research colleagues, Dr. V. Udall and Dr. Basu Mallick, to analyse the post-mortem records of University College Hospital over the last twenty years for the occurrence and distribution of cancer metastases. During this period it is safe to say that necropsies have been performed with standardized technique, that the type of case admitted to our hospital has not varied greatly, apart from some disequilibrium during the earlier war years, and that careful microscopical search of the main tissues in all instances has been steadily maintained. The results are given in Tables I and II.

TABLE I.—*Metastases in Liver and Lungs Grouped According to Relation of Primaries to Circulation. 910 Cancers from 6,047 Necropsies at U.C.H. over 20 Years*

Site of Primary Cancer	No. of Primary Cancers	Percentage Showing Metastases in	
		Lungs	Liver
Blood Flow Passes to Lungs First			
Breast	49	45	64
Uterus	37	11	24
Ovary	27	11	48
Kidney	19	31	40
Thyroid	10	70	20
Prostate	23	17	9
Blood Flow Passes to Liver First			
Lung	302	—	38
Stomach	144	15	68
Large intestine ..	129	12	40
Pancreas	48	15	58
Gall-bladder and bile ducts ..	31	19	45
Small intestine ..	6	—	33

They show that, whatever may be the immediate relationship of a primary tumour to the systemic or portal circulation, the liver becomes involved in secondary spread in a high proportion of cases. With cancer of the portal tract hepatic metastases regularly and convincingly outnumber secondaries within the lungs. The position with cancers elsewhere, with a

*Florence Blair-Bell Memorial Lecture delivered at the Liverpool Medical Institution on November 24, 1953.

TABLE II.—*Distribution of Metastases from Cancer of Alimentary Canal and from Cancer of Lung*

Metastases in	Cancer of A.C. (290)		Cancer of Lungs (302)	
	No. of Cases	%	No. of Cases	%
Liver	136	48	114	38
Adrenals	5	2	115	38
Brain	—	—	56	19
Kidneys	—	—	42	14
Bone	9	3	37	12
Pleura	8	3	24	8
Pericardium ..	3	1	18	6
Pancreas	26	9	16	5
Spleen	5	2	11	4
Peritoneum ..	49	17	8	3
Lung	38	14		

All other organs under 1% for metastases.

venous blood flow in the first instance to the lungs, is paradoxical. Indeed, in many cases metastases are less frequent in the lungs, where they would have been expected, than in the liver. In other cases, however, lung dissemination predominates over liver. We are thus confronted, at the very outset, with observations suggesting that the liver occupies a special place in the order of metastasis. It will be my endeavour to find out what lies behind this arresting fact.

Sooner or later all pathologists interested in cancer realize the limitations of human studies, and some of them turn to experiments on animals in the hope of achieving a more dynamic and perhaps direct attack on the problem. Since everyone does not agree about the value of animal studies it is worth while considering for a few moments some of the reasons given by cancer workers for this choice.

In the first place, they are quite sure that cancer behaves in animals in much the same fashion as in man, so that some, at least, of the lessons learnt from animal work may be applied with safety to human affairs. Secondly, it is possible to plan experiments whereby the fate of the main tumour or its metastases is influenced by treatment of various kinds. Another matter of some practical importance is the decision whether manipulations adopted during physical examination or surgical operation on the primary tumour increase or diminish the incidence of metastases. This concern certainly lies open to experimental test. Again, they would like to know if there are rules of behaviour shared by metastases and the parent tumour: here may be considered the possibility of an association between the type of tumour on the one hand and its speed of growth, resistance to local conditions, susceptibility to treatment with radiation or operation, and the likelihood of dissemination on the other. Into this category comes, too, the urgent question whether parent tumours

control the life of daughter tumours. And, finally, they wish to understand why certain tissues of the body are picked out with regularity or frequency by metastases. No doubt other equally good reasons could be added to the list, but I am sure you will agree that I have defined a programme which must convince any reasonable person of the need for experiments on cancer.

Without any more ado I shall pass to the experimental study of metastasis, especially as it concerns the liver, and endeavour to show you that progress is being achieved in this fascinating field of endeavour.

1. Invasion of Blood and Lymph Vessels by Cancer Cells

The first and most important step leading to the distant spread of a malignant tumour is invasion or infiltration of a blood or lymph vessel, the natural precursor to the process of embolism. Growth by contiguity may result in invasion of near-by tissues, and if this form of spread is ignored or defences fail there may be infiltration over an extensive territory. In no such case, however, can there be involvement of a far-distant organ; some motive force is necessary for the carriage of malignant cells to the new site of growth. Morbid histologists have long been aware of intrusion into blood and lymph vessels, for by means of serial sections cells can be traced from the outskirts of a tumour along more or less pliant and yielding tissue spaces to the environs of all kinds of vessels. Indeed, in some instances they have been followed through the wall of such vessels to the endothelial lining, where they have been caught in the very act of bursting through this limiting cellular membrane into the fluid contained within the tube. Histologists also recognize a not infrequent precursor of break-through in the form of thrombosis, which for a time seems to hold up the further progress of malignant cells. But all too frequently it encourages distant spread, since such a thrombus may be the breeding ground of tumour cells until it becomes overweighted and snaps off as an embolus. In this way a small mass of living tumour cells can be whisked away if the near-by circulation is still brisk, and the embolus is finally brought to rest where the blood stream is narrowed down to a set of capillaries with diameters smaller than the largest dimensions of the embolus.

But how do such tumour cells progress from their site of origin to vessels? Once again histologists have helped us by tracing columns or sheets of cells between the two focal points. However, this is not always possible, and we have to fall back upon the supposition that tumour cells possess powers of movement whereby they may cover not inconsiderable distances. Indeed, experimentalists have given us evidence of such motility. As long ago as 1863 the great German pathologist Rudolf Virchow stated that cancer cells as well as leucocytes dodge about like amoebae, and many tissue culturists have confirmed this observation (Carrel and Burrows, 1911; Lambert, 1916; Russell and Bland, 1933; Ludford, 1934). This movement actually has been photographed with the cinecamera, and the speed of movement calculated in some cases.

Enterline and Coman (1950) give average velocities for breast cancer cells of 0.7 μ per minute, or about 1 in. (2.5 cm.) in 10 hours, for carcinoma of the kidney up to 4.4 μ per minute, and for a mouse fibrosarcoma as high as 6.2 μ per minute. They have also observed that tiny clumps of carcinoma cells can move about as an amoeboid unit, in a fashion which recalls the astonishing progression of bacterial colonies studied some years ago by Cruickshank. Coman (1944) and his associates (de Long *et al.*, 1950; McCutcheon *et al.*, 1948) make out a case for the importance of adhesiveness between tumour cells in deciding infiltration. Break-away of single cells or tiny clusters of cells depends upon reduction of adhesiveness, which seems to be related in some fashion to deficiency in calcium content of the cells, particularly of their membranes. Here is a field of investigation for the biologist which is certainly related to the fundamental one of movement of cells in general.

The migration of tumour cells in living tissues now can be watched and photographed by means of ingenious techniques, chief among which is the Clark–Sandison and Algire chambers, applicable to the rabbit and the mouse. Before long it should be possible, by their use, to define with precision the factors which favour or prevent the local spread of neoplasms.

2. Carriage of Tumour Emboli in the Blood and Lymph Streams

The demonstration of tumour emboli within the circulating blood or lymph is the next step in the build-up of a theory of metastasis. It has presented many difficulties, since the perceptible growth of even the most active malignant tumour takes many days, weeks, or months, and, so far as we can tell, discharge of tumour cells into vessels is haphazard and on a relatively minute scale. To obtain samples of blood in which tumour cells are demonstrable is a matter of chance, with the odds well against the observer who aims at positive evidence. Success has come the way of several workers who injected blood from tumour-bearing animals into members of the same species (rats, mice especially) and obtained new tumours of the same type at the sites of injection (Blumenthal, 1929; Jonescu, 1931; Gross, 1932). In this way Flaks (1932) confirmed the presence of living tumour cells in lymph nodes receiving the lymph from a sarcomatous area, and could show that such cells were present in the lungs of the affected animals before metastases had made themselves known to the naked eye. From a careful study and review of the subject by Wagner (1938), it appears that the transfer to animals of tumour cells by the injection of heart blood or extract of lung vessels is successful only when such cells are demonstrable microscopically in these fluids. I can recall the excitement that I experienced as a young man when I found cancer cells in smears made from centrifuged blood obtained from a man with a rapidly spreading melanotic carcinoma.

We have no information about the number of tumour cells that must enter the blood of human beings, for instance, in order to produce metastases, but if facts obtained from animal experiments are applicable to man, then the effective number may not be very large. Kahn and Furth (1938) were able to transmit to inbred strains of mice a sarcoma, induced by the carcinogen benzpyrene, with 50 cells. Even more astonishing is the claim of these workers that certain strains of mouse leukaemia can be propagated by injection of a single leukaemic leucocyte into a vein. Obviously many variables come into the story, and a great deal will depend on the growth potentialities and resistance to changed conditions possessed by the tumour cells. Here again is a promising topic for investigation.

We do not know whether metastasis requires the continuous invasion of the blood or lymph stream by small or large numbers of tumour cells or whether discontinuous showers of cells suffice, provided conditions for survival and new growth of the metastasizing cells in their new surroundings are suitable. Some experiments on the influence of massage suggest that the cascading of cells may be important. In Japanese waltzing mice inoculated subcutaneously with a mouse carcinoma by Tyzzer (1913) manipulation and massage of the implanted tumour for a short period over several consecutive days increased the speed with which lung secondaries developed, and in some experiments greatly increased the number of metastases in that organ. These experiments were carefully controlled. Confirmation of Tyzzer's experiments has come from Knox (1921, 1922) and Marsh (1927). We may well believe that the periods of rough handling of these tumours led to vascular invasion on a scale sufficient to induce successful implantation in distant organs. So, too, experiments on incision or partial removal of primary tumours (Clunet, 1910; Tyzzer, 1913) and on the increase of susceptibility induced by haemorrhage (Gaylord and Simpson, 1916) hint at the same sort of phenomenon, although the results are not so convincing as with massage. I agree very strongly with Professor R. A. Willis in his plea for careful experiments on this and allied matters.

But the most persuasive evidence comes from the demonstration (1) that deliberate inoculation of the circulating blood with living tumour cells is often followed by the manifestation of tumours of the same type in various organs of the inoculated animal, and (2) of the need for a break-through into the blood stream of cells from the primary tumour. In support of the first thesis we have the old experiments of Cohnheim and Maas (1877), which showed that finely minced periosteum from rabbits, dogs, and hens injected into the jugular vein lodges as emboli in the lungs and for a time grows there, only to disappear in a few weeks. Cohnheim saw in these observations support for the origin of cancer metastases. Some years later Levin and Sittenfield (1910) and Gussio (1912) carried out with increasing care, as the pitfalls were realized, inoculation experiments which gave convincing support to the embolic theory of secondaries. Modern work has confirmed the pioneers' results. Even more illuminating are the experiments of Weil (1913) with the Flexner–Jobling rat sarcoma. This actively growing neoplasm can be transmitted from one animal to another by means of subcutaneous inoculation but fails to metastasize spontaneously. If suitable emulsions of the sarcoma be injected intravenously into rats with large subcutaneous tumours then a high proportion of these animals develop lung tumours. In other words, when tumour cells gain access to the veins of tumour-bearing animals metastasis follows. Weil concluded that the absence of spontaneous secondaries is due to failure of the primary growth to effect vascular invasion. We now know that this is an over-simplification of the story; nevertheless blood invasion is indispensable if a tumour is to spread to distant parts.

3. The Development of Metastases

For the development of metastases in an organ such as the liver there must be: (1) the impaction of living tumour cells within the blood vessels, especially the capillaries, of that organ; (2) the initiation of a new focus of tumour growth at the site of impaction; (3) the invasion of the perivascular tissues of the organ by new tumour cells breaking through impacted vessels. Each of these stages has been established by means of animal experiments, and there is equally impressive evidence from human experience.

The frequent impaction of tumour cells in various organs, especially the lungs, was convincingly established by Schmidt (1903) and confirmed by a host of pathologists. In the course of a careful microscopical study of 45 cases of abdominal cancer he found 15 with lungs either free from metastases or showing at the most minute white rice-shaped thickenings, which proved on microscopical examination to be blood vessels obstructed with cancer cells. In all such cases small collections of tumour cells were discovered within the smallest arteries or in the capillaries, either free or enclosed within thrombi. Some of these collections displayed indistinct broken-up nuclei and fused, homogeneous, poorly stained masses of cytoplasm—signs that the cells no longer survived. Others presented mitotic figures and were certainly growing. Occasionally tumour cells entirely filled vessel lumina and formed long columns extending from arteries to capillaries and even to veins. Spread through vessels to perivascular tissues could also be made out and from these areas could be traced the origins of true metastases. Schmidt concluded that the transportation of tumour cells to small lung arteries occurs with great frequency, but that only a small proportion of these passengers are transformed into secondaries. The bulk are killed off by encapsulation with red corpuscles and leucocytes or by the organization of the thrombi which rapidly enclose them.

I would repeat that the studies of Schmidt are exemplary and have never been surpassed. Though chiefly concerned with tumour emboli in the lungs they are applicable to other organs, with certain slight reservations. In the case of the liver, for instance, it is my experience that thrombi around impacted tumour masses are by no means common—an event not altogether unexpected when one recalls the part played by the liver in the prevention of blood coagulation by its synthesis of heparin. As an instance of the extraordinary fashion in which tumour cells may grow within blood vessels before breaking through the endothelial barrier let me recall a case described by the Canadian pathologist Horst Oertel (1935). A primary pyloric carcinoma came to necropsy without any obvious signs of metastases. Many organs, but especially the liver and the lungs and to a less extent the right adrenal, bone marrow, and bodies of some dorsal vertebrae, and the dura mater, showed widespread microscopical cancerous masses confined wholly to the blood vessels. The tumour cells had been growing alongside the circulating blood in these localities without displaying any aggressive tendencies for the closely associated tissues.

A further instance of the same sort of event, but this time deliberately induced in animals, are the experiments of the Japanese investigator Takahashi (1915–16) carried out at the Imperial Cancer Research Laboratories, London, during the first world war. White mice were inoculated intravenously with 0.2 g. suspension of various mouse tumours and killed after the lapse of three weeks. In a number of animals no tumours were found within the lungs despite most careful search, but tumour emboli in various stages of degeneration and thrombosis were numerous. Leucocytes were present in considerable numbers around the tumour cells, but the endothelium of the enclosing blood vessels showed no evidence of proliferation. In those mice with lung secondaries after intravenous inoculation, degeneration was certainly not obvious in the tumour emboli and signs of tumour proliferation became apparent after three days. Both carcinoma and sarcoma were equally capable of producing lung metastases, but tumour strains differed widely in their ability to survive intravenous implantation. The majority of the strains used in these experiments grew when inoculated subcutaneously, but no relation existed between success on subcutaneous implantation and tumour take in viscera after intravenous injection. Takahashi concluded that variation in production of metastases is not so much the failure of neoplastic cells to make their way into the blood stream as their inability to survive and grow after arrest in the vessels of an organ.

Modern studies of dissemination in general are worth noticing before we consider special problems of liver metastasis. American investigators have been particularly active in recent years in the design of quantitative studies. Fresh confirmation has come for the belief that the number of emboli reaching a tissue is important in determining the success or failure of spread. Since the mortality of embolic cells is very high, a great number of these cells fail to establish themselves in the organs preliminary to initiating a locus of growth (Warren and Gates, 1936; Zeidman *et al.*, 1950). Zeidman *et al.* determined the number of living cells by means of vital staining with trypan blue, in suspensions of mouse sarcoma, injected such suspensions in serial dilutions intravenously into mice, and counted the pulmonary tumours 18 days later. Table III shows that the number of metastases is directly proportional to the number of viable embolic cells.

These investigators, too, maintain that the number of metastases is proportional to the duration of the primary growth; the longer the primary tumour exists, the greater is the number of metastases. This is not a matter of chance of invading blood vessels, for there is no reason to believe that the final size—that is, the amount—of a primary tumour is a measure of the likelihood of metastasis. Such factors as motility of cancer cells and their power of destroying and overcoming natural defences must play an important part,

TABLE III.—*The Number of Metastases is Directly Proportional to the Number of Viable Embolic Tumour Cells. Mouse Sarcoma (Zeidman et al.)*

No. of Mice	No. of Viable Cells Injected Intravenously	Average No. of Pulmonary Tumours
10	104,400	11·5
10	19,800	2·5
8	5,400	1·7
10	900	0·3

but so far no quantitative methods have been invented for testing these propositions. I believe that this kind of investigation would give valuable returns.

4. The Liver as a Site of Metastasis

I must now turn from my general discussion of metastasis to consider the special problems of liver involvement.

Let me remind you, first of all, of the more obvious mechanical factors which contribute to the formation of secondaries in this organ. If cells from the parent tumour reach the portal blood then they will behave as emboli which lodge in the smallest portal venous radicles within Glisson's capsule or, if very small, they may even penetrate the liver lobules before coming to rest within the sinusoids. Since there is a rich anastomosis between the lobular sinusoids block is not a serious matter, and cancer emboli are unlikely to experience oxygen deficiency from purely mechanical reasons. Indeed, many observers have commented upon the ease with which these cancer cells grow and spread, sometimes for considerable distances. Moreover, they seem to seek out fresh and larger venous channels, as Willis reminds us. Each new break-through adds further opportunities of spread and encourages new cycles of growth. The risk of cells being carried away from the liver to the lungs by the hepatic venous blood has also to be faced and sometimes the lymphatics are also concerned in spread. Metastasis to the liver thus is fraught with great potentialities for catastrophe.

Investigation of the hepatic circulation has brought to light two strange properties which must be taken into consideration. For some years now we have gradually become aware of the importance of streamlining in the flow of liquids and gases. Flow of blood in the portal vein of animals is certainly streamlined, and it appears that portal blood from the stomach and spleen passes to the left portion of the liver and that from the greater part of the intestines is directed to the right half of the organ (Copher and Dick, 1928). Whether these rules can be applied to man seems doubtful if one considers the distribution of secondaries in the liver. Walther's and our experience engenders no enthusiasm for the view, although it is true that one sees specimens from time to time which suggest the influence of streamlining on distribution. More careful studies are badly needed before we can finally assess the position.

The second feature that cannot be ignored is the existence of territorial peculiarities in the blood flow through the liver and the presence of arteriovenous anastomoses. The former have been established in some laboratory animals by Daniel and Prichard (1951) by the use of cinephotography. These workers have demonstrated curious channels of direct flow from hilum to hepatic vein and have studied some of the factors which modify them. What part they may play in metastasis can only be guessed at. Arteriovenous anastomoses still have to be established in the human liver, but there is little doubt about their existence in some animals. Wakim and Mann (1942) and Seneviratne (1949–50) have found them in the transilluminated liver of the rat and mouse. Prinzmetal and his co-workers (1948) have shown that minute glass spheres up to 150 μ diameter can pass through the liver when they are introduced into the portal vein and be recovered from the lungs. Dr. Basu Mallick has confirmed these observations in my department. It is tempting to conclude that this phenomenon explains the absence or paucity of metastases in the liver that puzzles the pathologist from time to time when the lungs and other organs are the sites of secondaries.

But whatever may be the outcome of this kind of investigation all of us who have kept records of the distribution of tumours agree that the liver is an organ with some kind of predisposition for secondary carcinoma. From Table I emerges the fact that primary cancers make a habit of involving that organ, no matter what may be their relationship to the systemic and portal circulations. Nearly 70 years ago Stephen Paget (1889), in recording 735 fatal cases of carcinoma of the breast in which necropsy had been performed, noted that the liver was the seat of secondaries in 241 cases, whereas the lungs were involved in about 70, the kidneys or suprarenals in 30, and the spleen in only 17 instances. For this and various other reasons he adopted the idea put forward some years previously by Langenbeck, in Germany, of cancer cells requiring congenial soil if they are to live and grow. The "soil" idea, as a first approximation, ought to be a profitable hypothesis for further investigation, but it must be reluctantly confessed that it has led to little action though much speculation (Willis, 1952; Coman, 1953). I would like to direct your attention to several experimental studies which I think are full of interesting suggestions.

Some Experimental Studies

In 1932, Foulds, of the Imperial Cancer Research Fund, London, found that 92 rabbits with intramuscular implantations of Brown–Pearce tumour had developed secondaries in 25 instances. The adrenals were involved in 16, the kidneys in 14, the eyes in 11, the liver in 3, and the lungs in 2 animals. Intravenous inoculation of 71 rabbits with suspensions of this tumour resulted in embolic tumours in 60 animals, the growths being most frequent in the kidneys, adrenals, and eyes, and less frequent in the liver and lungs. When 34 rabbits were vitally stained with trypan blue before intravenous inoculation with the tumour suspension, growths were obtained in 30 animals, 17 of which showed splenic tumours. This was a surprising result, since at no time were tumours encountered in the spleens of unstained rabbits. By means of vital staining, therefore, Foulds had depressed the resistance of the spleen to tumour growth, and the organ now became a suitable "soil" for the ripening of the seed. Naturally enough, he suggested that the reticulo-endothelial elements might be the cellular basis of this splenic resistance, and it is not unreasonable to conjecture that these cells are concerned—as they are with resistance to many infective agents—with cancer resistance in general.

The likelihood of a cellular factor in resistance recalls the older experiments of Jones and Rous (1914), who showed that, by stimulating mechanically the peritoneum of mice by injections of kieselguhr, the growth of inoculated tumour can be encouraged at such points of irritation, for cells are quickly supported and nourished where a very cellular connective tissue is induced by the irritant. Here we are dealing with a phenomenon which may be allied to that recognized by Schmidt in the growth of metastases, but, taken in conjunction with Foulds's results, it suggests a dual mechanism of resistance to, and support for, cancer cell growth.

The "Soil" Hypothesis

Highly significant experiments planned to test the soil hypothesis have been carried out by Coman *et al.* (1949). A squamous-celled carcinoma of domestic rabbits—labelled V_2—has been discovered which disseminates regularly to adjacent lymph nodes, occasionally to the lungs, but rarely elsewhere. If suspensions of this tumour are injected intravenously, extensive cancerous infiltration of the leg muscles often develops thereafter in 65–86 days. It would seem that if large numbers of V_2 cells are able to reach the muscles they have no difficulty in establishing themselves there and producing secondaries. Yet observations on natural spread encourage the idea that muscle is an unfavourable soil for this tumour.

Again, if cancer cells from V_2 are injected into the left side of the heart they produce metastases everywhere. Apparently when these cells reach the left side of the heart in any number they will induce secondaries in any kind of tissue. In other words, they must first escape being trapped in the lungs, for even heavy suspensions of tumour cells injected into the right heart or femoral vein fail to give metastases elsewhere than in the lungs. These interesting experiments show the need for assessing the value of protective and mechanical factors before resorting to hypothetical explanations. However, this is not all of the story, for there are tumours such as the Brown–Pearce carcinoma of the rabbit, whose cells can pass through the pulmonary

labyrinth without delay, producing widespread visceral metastases, among which liver secondaries stand high. Arteriovenous anastomoses in the lungs (Prinzmetal *et al.*, 1948) no doubt would afford a rational basis for these results, but such anastomoses cannot explain why some tumours pass through rapidly and others not at all. Here is a further problem for study.

Finally, allow me to mention the experiment of Lucké *et al.* (1952), in which living V_2 carcinoma cells were injected simultaneously into the afferent blood vessels of the liver and the lungs of separate groups of rabbits in order to ascertain whether the resulting tumours grew equally well in these organs. In all of the 25 animals that were suitable for comparison the mean size of liver tumours exceeded that of lung tumours, whether the liver had been injected through the portal vein or the hepatic artery. Twelve days after the inoculation the liver tumours were about five times greater in volume than the corresponding lung growths, and after 35 days liver tumours were 100-250 times greater in size than those in the lungs. Lucké *et al.* conclude that tumours, once established, grow faster in the liver than in the lung, and they maintain that the liver is a better environment for supporting tumour growth than the lung. They obtained further support for this idea from 154 human necropsies, and with this reassurance they returned to the view that tissue environment or "soil" is of importance for metastasis. Coman (1953) likewise has reached the same conclusion in his most recent survey of the matter. On the other hand, Patey (1936–7) found that the Brown–Pearce carcinoma of the rabbit injected into the portal vein or systemic venous circulation gave many more secondaries in the latter instance than in the former. In neither case were metastases so numerous in the liver as in the kidneys, which appeared to be the most suitable "soil" for this tumour. Once again we find ourselves in the midst of conflict from which there is no escape but to admit the likelihood of a number of factors that condition the behaviour of each tumour.

Clearly it should be my final task to consider, for a few moments, some of the factors that might influence the growth of cancer cells in the liver with the object of defining more precisely the qualities of the hypothetical "soil." As a guide to this discussion let me postulate what I shall call "the principle of near-equivalence" for primary and secondary tumours. I refer to the necessity for conditions at the site of development of both these types being equivalent or almost equivalent in a strictly denumerable sense. We must be able to match such factors as the need for adequate oxygen supply, nutrition, hormones and vitamins, resistance mechanisms, and perhaps a great many other dimly perceived requirements—for example, Haddow's hypothetical growth factors—one against the other in considering parent and daughter growths. When this has been agreed upon local differences must surely indicate the predominance of one or other factor at that particular locality or the presence of something outside the group of agencies under consideration. Let us consider for a moment how we stand with some of these comparisons.

At least six notions may be offered in consideration of the liver as soil; some of these have been discussed by Willis (1934, 1948, 1952) and Walther (1948), the authorities on metastasis.

1. Oxygen Supply.—Is the oxygen supply of the liver different from that of other organs in which metastases are infrequent—for example, the spleen—or similar to that in tissues which are common sites for metastases, such as the lungs? Unpublished work in my own department by Dr. R. M. L. Mehrotra has shown the great variability in oxygen uptake in the rabbit's liver, and this agrees with observations made on the dog's liver by Blalock. I know of no accurate information about the oxygen uptake in the spleen, which, however, seems to be well off for oxygenated blood and is remarkably intolerant of anoxia. In the lungs, metastases first develop in the arterioles and arteriolar capillaries; the former, at least, contain venous blood. But many instances can be brought forward of the development of metastases in well-oxygenated tissues, so that, on the whole, the factor of oxygen supply cannot be important in the early stages of spread. Later on, when ischaemia intervenes, we know that growth of tumour cells may be seriously impeded and the cells destroyed.

2. Nutrition.—Willis (1934) has emphasized the rich carbohydrate supply in conjunction with poor oxygenation in the liver and is inclined to believe that these conditions will favour the survival and proliferation of cancer cells. I cannot accept his statement that oxygenation is poor, even though he is correct in pointing out that the hepatic artery is small and blood flow through its medium is restricted. We must take into consideration the part played by portal blood in supply of oxygen to liver cells even though it varies a great deal from one animal to another and from time to time. Nor should we forget that the hepatic artery makes up in speed of flow what it loses in volume. Payling Wright (1950) emphasizes the exceptionally high concentration of amino-acids reaching the liver from the alimentary canal and thinks this may be important in stimulating growth. I know of no experimental evidence that excess of nitrogenous units, or indeed of protein or any other food, stimulates the growth of tumour cells apart from a temporary acceleration. However, a depleted food supply appears to reduce the growth of certain tumours for a time. Of course, there may be qualitative factors which are more important than quantitative, but here again we are on uncertain ground.

3. Defence Mechanisms.—We have already noted a little evidence that reticulo-endothelial cells are important in resisting tumour growth. Unfortunately, no clear correlation between the amount of R.E. tissue and tumour resistance can be made out in such organs as lungs, liver, spleen, lymph nodes—all rich in R.E. cells—and kidneys, brain, bones, rather poorly off for R.E. cells. Perhaps when we know more about the factors that control R.E. cell activity we shall be able to explain resistance better. Such properties as speed of mobilization of cells, their adhesive tendencies—well marked in the case of the Kupffer cells of the liver, according to Rous—and their capacity to produce antibodies and to phagocytose must be of importance in deciding the qualities of soil.

4. Metabolites or secretory products formed in the tissues by tumour cells which may modify tumour growth. Willis (1952) discusses the information we possess about this matter, but it is indeed scanty when we consider organ differences.

5. Humoral defences, such as the local production and storage of antibodies, antibiotics, and the like, about which we can only guess.

6. Competition between the organ parenchymal and stromal cells on the one hand and invading cancer cells on the other. The late Dr. R. H. D. Short, in suggesting this possibility to me, proposed the view that what is left over after parenchymal cells have had their share of oxygen and food may be of vital importance for metastasizing cancer cells. In the later stages the position seems to be reversed, for the normal cells appear to be victims of the secondary tumour, undergoing degeneration and necrosis or atrophy. Stromal cells, in contrast, usually survive, and indeed may proliferate to give the scirrhous reaction.

No doubt other possibilities might be added to this somewhat indeterminate list; some of these I anticipate will be the concern as much of the normal cell and its environment as of the cancer cell. A start has been made in the analysis of variation in reaction to simple injury in tissues, from which has come the idea of fields of differing activity (Cameron and Mehrotra, 1953). Some such method of study might prove of value in the investigation of soil. Indeed, our concept of fields may turn out to be identical with that of soils, but only further research can settle the question.

Conclusion

My survey of the position of the liver in the hierarchy of metastasis has led us through a veritable icefield of disappointments and uncertainties heavily littered with crevasses of ignorance. But we need not

despair, since there is, I believe, a perceptible upward trend in our journey towards the goal of enlightenment. Comfort springs invariably from the labours of defining what we know and what we do not know, and many gloomy fears vanish in facing up to the unknown. My endeavour has been to define some of the problems of tumour spread which I believe would repay further investigation. I would plead, especially, for a change in attitude towards matters which are dismissed as insoluble. Why should we throw aside the problem of metastasis as hopeless? Why not strive to find ways of circumventing the growing tumour, by inhibiting or suppressing its powers of growth, by turning it aside into less innocuous channels, perhaps by throwing obstacles in its pathways of spread or even sacrificing healthy tissues in order to hold up the neoplastic invader by means of a "burnt earth" policy?

The search for effective chemotherapeutic measures must go on with the same enthusiasm and imagination displayed by Dr. Blair-Bell throughout his pioneering efforts in this great city of Liverpool. Ideas must be sought after and cultivated. We must not be afraid to attempt the impossible; no device or technique that holds out the faintest hope of discovery can be put aside without proper reference to the work in hand. Above all, I maintain that we teachers have a special duty to perform in firing the imagination and carefully fanning the flame of enthusiasm so that our young men and women may demand an entrance into the domain of cancer research. Perhaps it will be a supreme, audacious flight of youthful genius that will bring the answer to the riddle of neoplasia.

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TOXIC REACTIONS AFTER INTRAVENOUS SACCHARATED IRON OXIDE IN MAN

SUGGESTIONS FOR IMPROVED PREPARATIONS

BY

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It is six years since saccharated iron oxide was introduced for intravenous administration in patients refractory to or intolerant of oral iron (Nissim, 1947). Saccharated iron oxide may be said to have gone through the first critical years of its life with greater success than expected, and as regards the incidence of serious reactions following its administration it compares favourably with blood transfusion. Mild or moderate side-effects, however, have been reported rather too frequently. Holt (1953) made a plea for an assessment of the general toxicity of saccharated iron oxide. It is the object of this paper to give an account of my clinical experience with this preparation, albeit limited, and to submit the findings of various authors to careful analysis in the hope of shedding light on the type, incidence, and possible causation of these reactions. This is followed by suggestions of possible procedures to eliminate or minimize the incidence of such reactions.

Toxic Reactions in Animals

Toxicity studies of intravenous saccharated iron oxide in four species—namely, mice, rats, rabbits, and guinea-pigs—have shown conclusively that the observed toxic effects are associated with precipitation (Nissim, 1949, 1953a; Nissim and Robson, 1949). This iron preparation does not precipitate when mixed in any concentration with plasma or blood *in vitro*, but undoubted precipitation occurs *in vivo* above threshold doses, depending on the species. In the mouse and rabbit this threshold is around 45 mg. Fe per kg. body weight, above which *gradual* precipitation of the compound occurs. The iron precipitates in fine particles rather than clumps as occurs after colloidal ferric hydroxide (Nissim, 1949, 1953b). For this reason the toxic effects of saccharated iron oxide after such doses occur only after an interval when enough iron has precipitated. Precipitation occurs particularly in the lung capillaries.

Plasma iron and histological studies show that at a second and higher threshold—namely, 180 mg. Fe per kg. in the rabbit—saccharated iron oxide is followed by *abrupt* but partial precipitation, and is therefore capable of producing toxic reactions immediately after the injection of unusually large doses—for example, 360 mg. Fe per kg. The toxic effects are those of multiple embolism. No toxic reactions have been noted which could not be explained on the basis of pulmonary or systemic precipitation.

Types of Toxic Reactions in Man

My experience with saccharated iron oxide includes 28 patients, 19 in the first series (Nissim, 1947) and 9 in the second (Nissim, 1949). The total number of injections was 90, and the dose per injection varied from 10 mg. to 1 g. Fe. Two samples of saccharated iron oxide were used, one with an LD_{50} in white mice of 180 mg. Fe per kg. body weight, the other with an LD_{50} of 300 mg. Fe per kg. With the latter sample, which was used in the second series, doses of 200–300 mg. were given on 20 different occasions without toxic reactions of any kind. Only four mild or moderate reactions were encountered, all of which were in

the first series and followed doses of 1, 0.5, 0.5, and 0.25 g. Fe respectively. All these reactions came on 15 minutes to several hours after the injection, the interval being shorter with the larger doses. The reactions consisted of pyrexia with headache, pain in the back with weakness, or some degree of collapse with shivering and diarrhoea.

A review of papers on the clinical use of intravenous saccharated iron oxide, however, shows that toxic reactions fall into two groups, early and late. Early reactions usually occur immediately after injection, and certainly within the first ten minutes, while late reactions occur usually one-half to six hours after the injection. The reactions so far reported by the various authors are listed in Table I under the headings of early and late. A number of observations regarding the two types of reaction can be made.

TABLE I

Early Reactions	*Late Reactions*
Symptoms of pain:	Dizziness, lightheadedness, vertigo, and difficulty in standing upright
Headache	Weakness
Pain in arms and shoulders	Cold feeling, chilliness, rigors
Pain in chest (anginoid)	Temperature—103° F. (39·4° C.)
Pain in lumbar regions	Sweating
Pain in sacral regions	Nausea, vomiting, anorexia
Pain in front of thighs or back of legs	Diarrhoea
Symptoms suggestive of sympathetic stimulation:	Generalized urticaria or papular rash (in children)
Tachycardia and palpitation	Vague discomfort, tight feeling of skin all over body
Pallor	Tightness in chest
Faintness	Headache
Symptoms suggestive of para-sympathetic stimulation:	Pains over stomach
Feeling of heat or intense burning all over body	Pain in abdomen: may be associated with rigidity
Sweating	Pain in chest (pleuritic)
Lacrimation	,, ,, lumbar regions
Nausea	,, ,, arms
Irritation of throat and coughing	,, ,, legs and feet
Bronchospasm	Collapse, with grey colour, tachycardia, pulselessness, and subnormal temperature in severe cases
Dyspnoea	
Symptoms of circulatory collapse:	
Cyanosis	
Low blood pressure	

Early Type

Reactions of the early type are by far the more common, and occur even after relatively small doses—under 100 mg. Fe (Kartchner and Holmstrom, 1950). The late reactions are infrequent and occur particularly after large doses, their frequency increasing with the size of the dose (Ramsey, 1950). Only once was a delayed reaction reported after a dose of 100 mg. Fe (Mooney, 1950). From publications which record the time of onset of reactions, the incidence of early toxic effects varies from 0 to 10% of all injections (Govan and Scott, 1949; Briscoe, 1952) and seems to depend on the sample used. Thirteen cases of delayed reaction have so far been reported in this country (Table II), only three of which occurred after doses of less than 300 mg. Fe. Nine were reported by Ramsey, who attempted massive single injections of 300–900 mg. Fe. One delayed reaction occurred after a slow infusion of 1 g. Fe (Slowik, 1950). In America, Briscoe reported only "a few" reactions of delayed onset out of a total of 57.

It is of interest that in both my series of cases (Nissim, 1947, 1949) and that of Slack and Wilkinson (1949) the incidence of reactions was far less than that reported by later authors using commercial samples. In all three series "analar" sucrose was used in the preparation of the iron-sucrose complex, and the samples were fresh—that is, the period of time from manufacture to injection was short. It seems quite possible that both factors are responsible for increase in incidence of reactions, but the purity of sucrose seems to be a particularly important point (see below).

A woman who was treated at Guy's Hospital with 100 mg. Fe of one commercial sample of saccharated iron oxide responded with a typical anginose type of pain in the chest, down the arms, and also in the small of the back after each injection. The pain came on immediately at the end of the injection and lasted two to three minutes. When the same dose of saccharated iron oxide prepared from "analar" ingredients was given on a following day, there was no toxic reaction whatever. On the third day the patient was given another commercial preparation, prepared in the same way as the second sample (Nissim and Robson, 1949), except that the sucrose was not this time of "analar" standard. Exactly the same reaction supervened, and this painful effect thus appears to be due to impurities present in commercial preparations.

Precipitation of Iron Oxide

As already pointed out, toxic reactions in animals are accompanied by precipitation of the compound in capillaries, a precipitation which may be abrupt or gradual. Although no histological evidence of precipitation is available in man, it seems reasonable to presume that the delayed toxic reactions occurring after large doses are due to precipitation, particularly as the clinical superiority of samples possessing high LD_{50} and high threshold of precipitation (Nissim, 1949, p. 138) seems to be established. Further, this type of delayed reaction (Table II) appears to be in no way different from that described by Goetsch *et al.* (1946) and

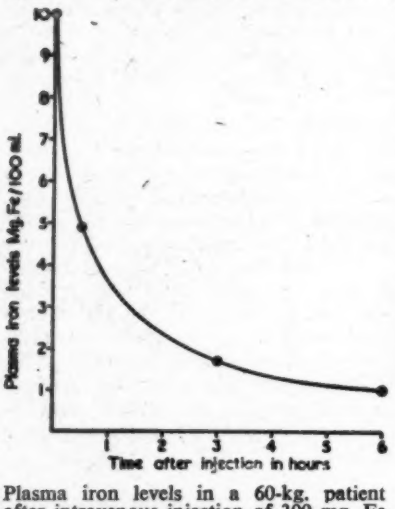
TABLE II.—*Incidence and Type of Reactions Following Intravenous Saccharated Iron Oxide*

Author	Preparation	No. of Cases	No. of Injections	Systemic Reactions			Doses in mg. Fe	Doses Causing Reactions in mg. Fe
				Early	Late	Total		
Briscoe (1952)	Feojectin	94	660	Most of 57 reactions	Few	57	30–200	—
Mitchell (1949)	Ferrivenin	Several	50	—	1	1	—	—
Mooney (1950)	—	24	—	—	1	1	—	100
Nicholson and Assali (1952)	Feojectin	16	203	?2	?1	2	150–400	200 and 400
Ramsey (1950)	Ferrivenin	11	16	3	9	12	300–900	300–900
Slowik (1950)	—	1	1	—	1	1	1,000	1,000
Barritt and Swain (1953)	Ferrivenin	1	1	1	—	1	100	100
Govan and Scott (1949)	,,	25	—	10%	—	10%	30–100	30–100
Hawkins *et al.* (1950)	,,	6	130	3 pts. on several occasions	—	3	20–100	—
Horrigan *et al.* (1950)	Feojectin	18	146	13	—	13	100–600	100–600
Kartchner and Holmstrom (1950)	,,	26	193	Most	—	35%	100–1,000	100–1,000
Librach (1953)	Ferrivenin and neo-ferrum	2	—	Several	—	Several	5–100	5–100
Scott and Govan (1951)	Ferrivenin and 2 other preps.	125	—	10–20%	—	10–20%	30–100	—
Sinclair and Duthie (1949)	Ferrivenin	23	—	1	—	1	50–200	200
Brown *et al.* (1950)	Feojectin and 2 other preps.	10	—	—	—	1	40–200	100
Cameron *et al.* (1951a)	Feojectin, ferrivenin, and 1 other prep.	6	52	—	—	0	50–200	—
Sinclair and Duthie (1950)	Ferrivenin and iviron	28	—	—	—	Occasional	50–400	—
Slack and Wilkinson (1949)	Own prep. and ferrivenin	60	—	—	—	1	25–200	200
Dickstein *et al.* (1952)*	Feojectin	80	198	—	—	21	25–100	25–100

* In children.

by Nissim (1947) after colloidal ferric hydroxide, a preparation known to precipitate in the plasma. If these toxic reactions following doses of 0.3–1 g. Fe (Nissim, 1947; Ramsey, 1950) are assumed to be due to precipitation, then the threshold of precipitation in man is considerably smaller than in the mouse and rabbit—namely, about 4–10 mg. Fe per kg. in the former as compared with about 45 mg. Fe per kg. in the latter.

The common early reactions in man described by many authors are largely different in type from late reactions and are not believed to be due to precipitation. Plasma iron levels in a 60-kg. patient following the injection of 300 mg. Fe gave figures of 10, 4.9, 1.7, and 1 mg. Fe per 100 ml. at 0, ½, 3, and 6 hours (see Chart), and conformed to the type of curve obtained in rabbits. There was even and total distribution of saccharated iron oxide in the plasma immediately after injection, and the iron showed a slow decline in the plasma according to a recognized semilogarithmic pattern for the uptake of colloidal substances by the reticulo-endothelial system (Halpern *et al.*, 1953; Biozzi *et al.*, 1953). Thus there is no evidence of precipitation in man following such doses normally, though this may perhaps occur in certain conditions—for example, severe reduction of the pulmonary capillary bed. Those factors present in certain samples which give rise to early toxic reactions in man cause no detectable toxic effects in animals, so that the superiority of samples regarding these early toxic reactions are not shown by their LD_{50} or by the absence of some typical toxic response.



Plasma iron levels in a 60-kg. patient after intravenous injection of 300 mg. Fe as saccharated iron oxide.

The anginal type of pain as well as the pain in the back seen among the early reactions, particularly in elderly patients, suggest ischaemia of poorly supplied viscera. The ischaemia may be caused directly by spasmodic action of the material on the coronary or renal vessels. Alternatively, it may be caused by dilatation of vessels in the splanchnic area with diversion of the blood thereto. The list of early reactions shows that sometimes the responses suggest sympathetic stimulation, at other times parasympathetic stimulation. It is of interest, however, that the injection of tetraethylammonium chloride in one case simultaneously with saccharated iron oxide did not prevent this painful type of reaction, but the injection of calcium gluconate in another diminished its intensity (Horrigan *et al.*, 1950). Only a proportion of people (10–20%) seem to be susceptible to these early reactions.

Perhaps the strongest support for the dual mechanism of the reactions is obtained from the paper of Ramsey, who gave doses of 300–900 mg. Fe to 11 patients. Delayed reactions, which are extremely rare in doses under 300 mg., occurred here in 9 out of 16 injections (56%). Early reactions, on the other hand, occurred only in three out of 16 injections (19%), a frequency not much higher than that reported after the usual smaller doses. More interesting still is the fact that two of the latter three patients, having recovered from their transient early reactions, showed the delayed type of reaction several hours later, after a period entirely free of symptoms between the two episodes.

Toxic Reactions in Tuberculous Patients

Librach (1953) described two cases of toxic reactions to intravenous saccharated iron oxide in patients with pulmonary tuberculosis and discussed the possible mechanisms of iron intoxication in detail. It is pointed out here, however, that a different mechanism may have operated in these two cases, both of which had a severe involvement of the lungs with the tuberculous process. One was described as a case of chronic pulmonary tuberculosis complicated by amyloid disease and massive albuminuria; the other had tuberculous bronchopneumonia. In both cases severe limitation of lung capacity was likely, with marked diminution in the lung capillary bed. This may be an important point in the consideration of the mechanism of toxicity of intravenous saccharated iron oxide. Animal studies show that saccharated iron oxide is most likely to precipitate in the lung capillaries after intravenous injection (Nissim, 1953a), since it is through these capillaries that the iron passes before being adequately diluted in the blood. Another favourite site of precipitation is the kidney (Nissim, 1953c), because of the increase in iron concentration following plasma filtration through the glomeruli. Saccharated iron oxide can precipitate both immediately and gradually above certain threshold concentrations, and it seems reasonable to suppose that such precipitation is more likely to occur with small doses when there is severe diminution in lung reserve. This is a point worth bearing in mind when intravenous iron is considered for such cases. Although in Librach's cases the early reaction may have been due to impurities, as discussed previously, the epileptiform fit and pain in the chest lasting for 24 hours in Case 1 and the dyspnoea and cyanosis in Case 2 are compatible with reaction of the second type, in this case due to abrupt precipitation. The restriction in the lung capillary bed may have been made worse by the previous two injections given without untoward effects.

Librach invoked the iron transport mechanism of the β-globulin-fraction iv–4(8) of Cohn, or siderophilin, as being partly responsible for the occurrence of iron reactions in these subjects. The work carried out on plasma iron following saccharated iron oxide throws doubt on this hypothesis. Klopper (1951) found that toxic effects arose only when the iron-binding capacity is exceeded in the individual injections. It is pointed out here that siderophilin cannot be involved in the transport of the iron of saccharated iron oxide to any extent, since calculation shows that the iron-binding capacity of the total plasma in an adult is only about 16 mg. Of this total a third is already bound to iron, so that doses in excess of 10 mg. should give rise to toxic reactions. This is evidently not so, as shown by the plasma iron levels of 5–10 mg. Fe per 100 ml. maintained for a period of hours without the slightest toxic manifestation.

Saccharated iron oxide is a colloidal compound the iron of which is not split off easily. Its estimation in plasma requires the use of much larger quantities of HCl than is usually employed (Nissim, 1953b), and this accounts for the much lower plasma iron figures obtained by previous workers following intravenous saccharated iron oxide (Cameron *et al.*, 1951b). The proportion of plasma iron estimated by the usual methods—for example Laurell's (1947) method—after injection of saccharated iron oxide is not greater than the proportion before injection (20%), suggesting that little splitting of the compound, if any, takes place *in vivo*. It is possible that certain preparations of saccharated iron oxide contain a small proportion of diffusible or ionic iron as impurities, but until this is shown to be the case toxic reactions due to oversaturation of siderophilin remain hypothetical. Cameron *et al.* (1951a) found that following injections of saccharated iron oxide the total iron-binding capacity of serum was reduced but never approached zero, so that the belief that saccharated iron oxide remains unsplit in the plasma finds additional support here.

Allergy

Librach further believed that the question of allergy is important. Evidence for natural hypersensitivity to impurities in certain commercial samples exhibiting itself in the early and usually transient type of reaction has already been presented. These impurities may have the nature of histamine releasers, as suggested by the bronchospasm reported in some patients (Sinclair and Duthie, 1949). Acquired allergic hypersensitivity to a component or impurity in the preparation, however, is another matter. The repeated injection of saccharated iron oxide in animals has never resulted in allergic manifestations (Cappell, 1930; Nissim, 1953). In man the incidence of reactions of the early type is not greater after later injections than after first injections. The incidence of the delayed type of reactions decreases if anything with repeated injections (Ramsey, 1950) apparently owing to hypertrophy of the reticulo-endothelial system (Cappell, 1930). The occurrence of a reaction in a patient following an injection of saccharated iron oxide when previous doses were well tolerated may possibly be due to differences in batches of the preparation (Dickstein *et al.*, 1952). However, the occurrence of isolated instances of acquired hypersensitivity—for example, the case of Sinclair and Duthie (1949) and the two cases of Librach—cannot be ruled out, but on account of their rarity other possible causes must be considered—for example, change of batch—before such a hypothesis is accepted.

The suggestion put forward by Ramsey for the late reactions is interesting. He noted that they resembled in a striking manner those symptoms of paroxysmal haemoglobinuria from cold, and believed that they "may well be caused by sudden increased activity of the cells of the reticulo-endothelial system." To what extent overactivity of the reticulo-endothelial cells is by itself capable of producing toxic symptoms is a problem difficult to answer. The injection of colloidal dextran in *relatively* large doses or of vital dyes which are taken up by the reticulo-endothelial cells seems to be devoid of toxic effects. Saccharated iron oxide is certainly taken up by the reticulo-endothelial system, but it is also known that, in animals, saccharated iron oxide precipitates above a threshold level, and this seems the obvious mechanism responsible for the toxic effects in man after large doses. Other hypotheses lack experimental evidence.

Librach (1953) discussed "iron poisoning" in rather general terms, and included in his discussion cases of toxicity after intravenous saccharated iron oxide and after oral ferrous sulphate (Prain, 1949) without adequate distinction. It cannot be too strongly emphasized that, apart from completely ionized ferrous and ferric compounds, many iron preparations are in fact non-ionized complexes with entirely different mechanisms of toxicity, mechanisms which depend on the chemical reactivity and other properties of the whole molecule (Nissim, 1953d). Indeed, some preparations show different mechanisms in the causation of death at different dose levels. Discussion of toxicity must therefore be confined to the compound in question, unless it is shown that the compound is ionized either partly or wholly, when the mechanisms of toxicity for either ferric or ferrous ions may be invoked.

Reaction in a Fatal Case

In the fatal case reported by Barritt and Swain (1953) it seems fairly clear that the reaction was of the early type without evidence of precipitation. The absence of multiple emboli at necropsy and in the toxicity tests carried out on samples before and after injection seems to rule out this possibility satisfactorily. It seems likely that the mechanism of ischaemia discussed previously was responsible for the fatal outcome, especially on account of the post-mortem evidence of calcification of both coronaries with complete occlusion of the right artery. It is difficult, however, to assess the seriousness of the part played by intravenous iron, as such a patient may succumb to an attack of coronary occlusion even after a relatively mild reaction. It becomes obvious, nevertheless, that particular care should be observed with such cases.

Infants and children seem to tolerate saccharated iron oxide in relatively large doses—25–100 mg. Fe (Bramham, 1952; Dickstein *et al.*, 1952), in contrast to elderly patients, who tolerate it less well than normal adults (M. R. Jeffrey, 1952, personal communication). Reactions in children are mild. In a series of 198 injections in 80 infants and children, Dickstein *et al.* reported three cases of generalized papular rash, which suggest an allergic response. The rash lasted only for one day. All of nine febrile reactions were associated with one sample of the preparation and ceased when a fresh batch was used. Although these febrile reactions were delayed in onset (appearing in about two hours) and lasted some two to three hours, it is difficult to attribute them with certainty either to allergy-producing impurities or to precipitation.

Conclusions

Sucrose and other substances used in the preparation of saccharated iron oxide should be of high standard.

There is evidence from histological studies in animals injected with two- to three-year-old solutions of saccharated iron oxide that the character of the compound undergoes slow alteration in solution with increase in diffusibility, and its uptake by fibrous-tissue elements becomes marked. This change may be associated with increase in toxicity or allergy-inducing properties in man and may be prevented by keeping the compound and ampoules in powder form just as practised with intravenous barbiturates. If this reduces the incidence of toxic effects the additional cost of the procedure would be justified.

It may prove possible to separate impurities from solutions of saccharated iron oxide by dialysis. Further, saccharated iron oxide may consist of colloidal particles of various sizes, and fractional ultrafiltration may give a more uniform preparation of reduced toxicity.

The extent to which these suggestions are compatible with the cost of manufacture can be decided only by the various firms engaged in the preparation of saccharated iron oxide. The use of analar ingredients seems to be the easiest step, and this is believed to have been already adopted by some drug firms.

Summary

The frequency and type of toxic reactions following intravenous saccharated iron oxide are discussed. A review of the incidence of these reactions in the hands of various workers is presented.

Reactions are of two types, early and late; a list of the toxic effects in the two types is given. Early reactions are believed to be due to individual hypersensitivity to impurities apparently present in commercial (*B.P.*) sucrose and may be allergic in type. Particular care should be taken in patients with arteriosclerosis, as the frequent transient anginal type of pain and back pain suggest ischaemia of the myocardium and kidneys.

The majority, at least, of delayed reactions are believed to be due to the gradual precipitation of the compound as occurs in animals following large doses. Some precipitation of saccharated iron oxide may possibly occur immediately after injection if the capillary bed in the lungs is greatly reduced by disease or the preparation injected too rapidly.

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MANAGEMENT OF THE COMMON VARIETIES OF SCALP RINGWORM*

BY

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The differential diagnosis of the various types of scalp ringworm is of importance, since good treatment follows accurate mycological diagnosis. It is not necessary to have the result of mycological culture before treating any individual case. Considerable accuracy in clinical diagnosis can be achieved when one has, as a background, full knowledge of the various types of fungi which are endemic or epidemic in the area. One can simplify diagnosis and arrive at sound practical treatment by concentrating on the three, four, or five fungi which occur in the locality (Table I). In the North of Ireland there are four important fungi (Beare and Cheeseman, 1953), which accounted for 99% of 1,157 cases of tinea capitis seen between May, 1948, and December, 1952, and from which the responsible organisms were identified. These four fungi are *Microsporum audouini* (889 cases), *M. canis* (178 cases), *Trichophyton sulphureum* (55 cases), and *T. discoides* (24 cases). Three other fungi were encountered during this period—namely, *T. mentagrophytes* (8 cases), *T. equinum* (2 cases), and *T. schönleini* (1 case).

TABLE I

Fungus	Animal	Inflammatory Reaction	Wood's Light	Outbreaks	Treatment
M. audouini	None	None	Green fluorescence	Large epidemics often occur	*X*-ray epilation
M. canis	Kitten	None or moderate	Green fluorescence	Usually small outbreaks affecting about 5–15 children	Fungicidal ointments
T. sulphureum	None	None	Nil	No very large outbreak so far reported, but general incidence is apparently increasing	*X*-ray epilation
T. discoides	Calf	Severe	Nil	Individual cases or 3–4 in a family	Starch poultices; extraction of loose hairs with forceps; soothing local applications

An easy and useful practical classification of the four common types of tinea capitis is by division into Wood's-light-positive and Wood's-light-negative cases, and subdivision of each of these two groups into human and animal types of fungi, as follows. Wood's-light-positive: human, *M. audouini*; animal, *M. canis*. Wood's-light-negative: human, *T. sulphureum*; animal, *T. discoides*. These four main groups are discussed in turn.

M. audouini Infections of the Scalp

Recently there has been considerable discussion regarding the possible effectiveness of local ointment treatment for cases of tinea capitis due to *M. audouini*. Among the best results are those obtained by Schwartz *et al.* (1946), who, in a carefully conducted and very practical trial, claimed 274 cures out of 445 children treated with local medications within a 16-months study period (61.6%). Similar results were obtained by Barlow *et al.* (1950). It would be fortunate indeed if we could cure this type of scalp ringworm by local application of a simple ointment, but the conservative treatment of this variety requires certain ancillary measures which the average general practitioner or school medical officer would find extremely difficult to carry out.

Treatment with Ointment.—The disadvantages of local ointment treatment for this condition, even assuming that this treatment is really effective and that cure is not spontaneous—and this is still in debate—include the following. (1) Treatment has to be carried out by reliable trained persons and not left to parents or friends. (2) During the time that the child is having treatment, unless supervision is very close, he will be infectious. (3) The failure rate over a reasonable period, such as six months, is considerable, as can be seen from an examination of the various clinical trials so far reported. (4) Some of the cures seem to have acted by producing local kerion-like reactions. I have seen these "artificially produced kerions" leave permanent scarring. (5) It is usually necessary to shave the children's scalps. (6) *X*-ray therapy centres are still required to deal with those children who fail to respond to ointment therapy.

Advantages of X-ray Epilation.—(1) *X*-ray epilation for this form of scalp ringworm offers an almost 100% certain cure within a period of four to six weeks. The treatment can be carried out in less than an hour, it is completely painless, and from all practical points of view it is safe if used by people who have been thoroughly trained in this method of treatment. Hair regrowth in boys is complete in six months. (2) The amount of co-operation required between hospital staff and parent is reduced to a minimum. One has only to get written consent, have the child for an hour, and then, no matter what the parents do subsequently, that child will almost certainly be free of infection in a month. (3) Unruly and obstreperous children can be conveniently managed under a light general anaesthetic.

Steps Taken in a Series of Cases

In 1948 it was estimated that there were about 1,000 cases of *M. audouini* scalp ringworm in the North of Ireland. The following steps were taken to deal with this campaign. (1) Examination of all schoolchildren within the affected areas by a nurse using Wood's light. In Belfast 50,000 such examinations were made and 225 cases found; 100 further cases were discovered among relatives of non-school age. (2) General practitioners and school medical officers were encouraged to refer their cases to a ringworm centre. (3) Wall maps were made out and coloured pins inserted to denote the homes of infected children. (4) An adequate

*Based on a paper read in the Section of Dermatology at the Annual Meeting of the British Medical Association, Cardiff, 1953.

follow-up system was started. Infected children were regarded as a danger to the community. (5) Infected children were kept from school, mainly because it was felt that this gave control of the case. If a child is not allowed to go to school then most mothers, however obstinate, will eventually yield and have whatever treatment is advised.

One amusing but troublesome difficulty was encountered over this decision to keep infected children away from school. So many children were away from school—in some cases all the children living in a street had ringworm—that a child who was not infected felt "out of it all." A market in ringworm was started by the more enterprising sufferers from this condition, and infection was sold at a price which at the height of the market reached sixpence a rub. To solve this problem the school authorities opened a special ringworm school : this allowed us to retain control of the case.

Results

About the summer of 1951 a very appreciable drop in the incidence of infection was noted, and by August or September of that year the falling off of cases was considerable. Only two cases from the Belfast and Newtownards areas were seen in 1952, and only one isolated case in 1953.

There is undoubtedly some as yet unknown factor which determines the virulence of *M. audouini*, and therefore the incidence of tinea capitis due to this fungus. Kligman (1952) found great difficulty in inoculating experimentally the scalps of children maintained in an institution in Philadelphia. He expressed the opinion that this disease was not so infectious as had had sometimes been claimed. I cannot agree with this, and the following data indicate the high degree of infectiousness in practice. The incidence of ringworm during the epidemic period in the town of Newtownards was 12%, 368 children from a total child population of 3,000 under the age of 17 years being affected between January, 1948, and August, 1949 (27.2% of the male school population were infected). In another epidemic in the North of Ireland which occurred in a residential school, 31.6%—or 116 children out of a population of 367—were affected (Walby, 1952).

M. canis Infections of the Scalp

During recent years we have carried out few *x*-ray epilations for cases of tinea capitis due to this fungus. Various authors in the past have stated that the majority of *M. canis* infections of the scalp clear spontaneously, and that *x*-ray epilation is not always necessary (Lewis and Miller, 1934; Lewis, 1935). When *all* the non-epilated children who had been seen in 1948 with scalp ringworm at the Royal Belfast Hospital for Sick Children were recalled during the early months of 1949 none were found to be infected by *M. canis*. These children represented a very mixed group of infections, and it can be safely assumed that some of them were originally cases of *M. canis* infection. It was therefore apparent that the great majority of these infections must clear quite quickly and spontaneously. However, during the time when we were primarily concerned with *M. audouini* it was felt that, from the point of view of the welfare of the community, all cases of non-inflammatory scalp ringworm should be subjected to *x*-ray epilation. Consequently a large number of cases of *M. canis* infection were epilated during 1949–51.

It is possible to make a clinical differentiation between *M. audouini* and *M. canis* infections in the majority of cases (Beare and Cheeseman, 1951).

Treatment

So far as I am aware, no properly controlled experiment estimating the time saved by subjecting children with the *M. canis* variety of scalp ringworm to *x*-ray epilation has been carried out. Useful information can be obtained by comparing the duration of infection in groups of children presenting with different inflammatory reactions. The inflammatory varieties cause no undue worry, and if it can be shown that the non-inflammatory cases, if not epilated, clear as quickly or nearly as quickly, then this would seem to be a strong indication not to use *x*-ray therapy with its attendant troubles and subsequent temporary alopecia for any case due to this fungus.

In 1949–50 there were 90 cases of *M. canis* scalp infection, and of these 42 were epilated. For the most part these were the non-inflammatory cases. In 1951–2 there were 88 cases and 5 were epilated (4 in 1951 and 1 in 1952). There was no special selection of these five cases for epilation. Of the 83 non-epilated cases the attendances of 61 were regular enough to allow of analysis (the other 22 did not re-attend just when requested, though all were eventually re-examined). These 61 cases were analysed from the point of view of duration of infection, and it is possible to divide them into two groups according to the severity of the inflammatory reaction present.

All patients were treated simply by local application of Whitfield's ointment. Inflammatory reaction was absent in 27 patients and slight or severe in the remaining 34.

Duration of Infection

Table II shows the average duration of treatment, measured from the date when the patient was first seen to the date when judged to be clear of infection. In the group

TABLE II.—*Analysis of Average Duration of Time Between Date Patient First Seen and Date Infection Cleared*

	No Reaction	Slight to Severe Reaction
Number of patients	27	34
Mean duration (first seen—clear): days	57·00	47·59
Standard deviation of duration: days	22·33	26·83
Standard error o mean: days	4·30	4·60
Difference between means: days	9·41	
Standard error of difference: days	6·75	
Difference ÷ standard error	1·4	

with no inflammatory reaction the average duration of treatment was approximately 57 days, while in the group with slight to severe reaction it was 48 days. Although these averages do suggest that the condition takes longer to clear in patients with no reaction than in patients with reaction, the average difference is only about nine days, and, moreover, could quite easily have arisen by chance. (The table shows that the difference is less than twice its standard error and would be described as "not significant" at the conventional 5% probability level.)

Since the two averages are not significantly different, it is legitimate, for these data, to pool the two reaction groups to arrive at statistics for the complete group of 61 patients. When this is done the average duration of time between the date when the patient was first seen and the date when the infection was cured is approximately 52 days, and the series has a standard deviation of approximately 25 days. The latter suggests considerable variation between individual patients.

The absence of a real difference in duration of infection in the two groups from the time the patients were first seen implies that, if both types of case react similarly to the treatment given, there is no evidence, from these data, of a significantly longer duration in the patients with no inflammatory reaction compared with those with slight to severe inflammatory reactions.

Table III is an attempt to arrive at average durations of infection from time of onset—estimated at history taking—to time infection was clear. There is a marked similarity between the durations so obtained in the two reaction groups. Where reaction was absent the average duration of the condition was only four days (approximately) greater than where reaction was present. Again the difference is insignificant at the 5% probability level. When the two groups are pooled it is found that the average duration of

TABLE III.—*Analysis of Estimated Average Duration of Infection Between Estimated Date of Onset and Date Infection Cleared*

	No Reaction	Slight to Severe Reaction
Number of patients	27	34
Mean duration (onset—clear): days	72·81	68·38
Standard deviation of duration: days	27·87	24·17
Standard error of mean: days	5·36	4·15
Difference between means: days	4·43	
Standard error of difference: days	6·78	
Difference ÷ standard error	0·7	

infection from the time of onset to the time cleared for the 61 patients was about 70 days, and the standard deviation about 26 days.

It must be pointed out that in Tables II and III the longer average duration is, in fact, found in the group which experienced no inflammatory reaction. In these data, however, the excess could easily be attributed to chance, but the numbers involved are admittedly small. In view of the results of this tentative examination it seems wrong to accept at this stage the suggestion that, other things being equal, there is a real difference in the duration of the condition between groups of patients with different inflammatory reactions.

One could expect to clear all cases of *M. canis* scalp ringworm with *x*-ray epilation in approximately four weeks, certainly six weeks (28 to 42 days). This would imply that probably a little over half of the children in the present series (irrespective of the intensity of inflammatory reaction) would have been rendered free of infection more quickly had they been epilated with *x* rays. Against this, however, must be balanced the fact that these children would have been bald for some four months, long after they would have been free of infection had they been treated conservatively, and the epilated girls, of course, would actually be socially unacceptable for longer than four months.

It is of some interest that the number of new cases seen each year showed little variation (1949, 42 cases; 1950, 48 cases; 1951, 42 cases; 1952, 46 cases), which is further support for the thesis that *x*-ray epilation is not necessary in this infection. Thomas (1953) also supports this view. One might advocate *x*-ray epilation for cases of *M. canis* infection in which there is a complete absence of inflammatory reaction. The longest duration one has seen of this variety of tinea capitis is 149 days (about five months). This was exceptional, and if this long duration could be predicted in any individual case *x*-ray epilation would probably be justifiable.

Many of the non-inflammatory *M. canis* cases which clear within six weeks or so are probably the result of a third or fourth transfer of the organism. Duncan (1948) has pointed out that *M. canis* infections undergo a limited number of transfers; for example, kitten to child A—to child B—to child C, and then the organism probably becomes avirulent.

Our routine now for *M. canis* scalp infections is local treatment with a fungicidal ointment. The advantages of using a rather sticky ointment such as Whitfield's probably lie in the fact that this prevents loose hairs and spores from falling in all directions, not only on to the child's environment, but also on to other parts of the child's scalp.

T. sulphureum Infections of the Scalp

Fifty-five patients with tinea capitis due to this fungus have been seen during the period 1949–52. This variety of ringworm has recently attracted considerable attention. Howell *et al.* (1952) have described 37 cases seen in Texas and California. Under Wood's light there is complete absence of fluorescence, but clinically these infections are often very much like those caused by *M. audouini*.

In the present series 36 of the 55 cases showed little or no inflammatory reaction. Eleven were classified as kerions. It is curious that these kerions were seen for the most part during the last year of the present four-year survey. Forty-one cases were seen within two months of onset of infection, but four had had the infection for more than one year, and one had had an infection for over two years. Two boys were affected to every one girl. The average age was 7, but there was a fairly even spread throughout the first 14 years of life. No adults with this infection of the scalp were seen.

In the North of Ireland the infection is practically confined to Belfast, and in general is probably a disease of large centres of population. There is no animal reservoir, and infection passes from patient to patient. There was a steady rise in the number of new cases seen each year (1949, 10 cases; 1950, 11 cases; 1951, 13 cases; 1952, 21 cases).

It has usually been extremely difficult to establish the source of infection, and indeed only once, when brother and sister were infected, was this possible. Extensive scalp infections were seldom seen, and the most usual picture was that of a single small scaly non-inflammatory patch, often like a mild seborrhoeic dermatitis, but with some broken-off hair stumps. Thirty-four of the 55 cases had only one patch.

In addition to the cases of tinea capitis, 16 cases of tinea corporis due to this fungus were seen. The areas most often involved were the face and neck.

Local epilation was used in preference to total epilation because so many cases had only one patch, but of 31 cases so treated 6 were failures. In these particular cases the infection appeared in the adjacent non-epilated hair. Eight cases had total epilation, and in one of these it was a failure. A few cases cleared without epilation, including the 11 with kerions. Treatments used when *x*-ray epilation was avoided included Whitfield's ointment locally and manual epilation of hair stumps. Since the infection is non-fluorescent under Wood's light this is a very tedious and unreliable procedure.

The treatment of choice for non-inflammatory infections is probably a whole-scalp epilation even when only a single patch is present.

T. discoides Infections of the Scalp

This fungus is the common cause of cattle ringworm in the United Kingdom. It causes an extremely severe local reaction which sometimes progresses to a chronic granuloma that may persist for six months or more and often leads to scarring and areas of permanent baldness.

Most Ulster patients first seek cure from the local charmer, and have a smouldering twig waved three times round the affected area on the night of a full moon. This procedure does much less harm than tincture of iodine, and the results are probably just as good. It is extremely doubtful whether anything we do can actually shorten the duration of a *T. discoides* infection. A possible exception to this statement is manual epilation of the loose affected hairs, using a small pair of forceps. For patients who can be admitted to hospital this procedure should certainly be carried out. Sticky starch poultices and removal of the affected hairs by this method are also of value. Symptomatic treatment is, of course, appreciated, since the condition is uncomfortable or even painful.

T. discoides infections can usually be differentiated from *T. sulphureum* infections by (*a*) the degree of reaction, which is so much greater with *T. discoides*; (*b*) a history of contact with infected cattle, which is always given for *T. discoides* infections; and (*c*) in the North of Ireland finding out where the patient lives: a non-fluorescent scalp ringworm from Belfast is *T. sulphureum* and from outside Belfast is *T. discoides*.

Conclusions

It is possible to differentiate the four chief varieties of scalp ringworm by simple clinical inspection and Wood's-light examination.

The presence of *M. audouini* represents a danger to the child community and a challenge to the doctor.

It should be possible to eradicate completely this variety of ringworm from a community. *X*-ray epilation should ideally be carried out at the child's first attendance at a dermatological clinic. All contacts in the home and school should be examined with Wood's light.

The importance of *M. canis* ringworm lies in its differentiation from the *M. audouini* variety. *X*-ray epilation is seldom indicated.

T. sulphureum is likely to cause great anxiety and trouble in the near future, since diagnosis of the non-inflammatory varieties is difficult, and the disease may last for years if untreated. *X*-ray epilation of the whole scalp is probably the best treatment in most cases.

It is very doubtful whether any procedure can actually shorten the duration of *T. discoides* infections, but symptomatic treatment is appreciated by the patient.

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ATELECTASIS AS A COMPLICATION IN ARTIFICIAL PNEUMOTHORAX

BY

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Since 1920 therapeutic pneumothorax has had a vogue which was certainly excessive at first, but lately the balance has swung the other way and some authorities seem to regard it as a dangerous procedure which should be used only in exceptional cases (Harris *et al.*, 1952; Jackson, 1952; Simmonds *et al.*, 1952).

Young (1949) believes that the cause of this trend of opinion is the fact that the technique seems so easy that it has been carried out by workers inexperienced in the proper selection of cases or in the finer points of its conduct. In the management of artificial pneumothorax (A.P.) cases the physician must be experienced enough to recognize the circumstances that demand the immediate termination of the pneumothorax treatment. Also, to give the best chance to his patients who need the help of an A.P., he must know what "complications", may be disregarded with reasonable safety. One such complication often appearing in an otherwise perfect pneumothorax is the occurrence of an area of atelectasis; and the object of the present investigation is to try to decide whether or not such an occurrence is an indication for suspending this type of collapse therapy.

Some writers have associated atelectasis occurring in an A.P. with such sequelae as progressive tuberculous disease (Rafferty and Shields, 1943), with relapse (Maher-Loughnan, 1950), and with tuberculous pleural effusions and empyemata (Houghton, 1950). On the other hand, Scadding *et al.* (1952), Foster-Carter *et al.* (1952), and Beric Wright (1952) have recorded satisfactory results in small groups of cases with atelectatic lobes or segments, while earlier writers (Brooks, 1938; Erwin, 1939) regarded its occurrence as a favourable event.

At the Cheshire Joint Sanatorium the clinical impression has long been that the occurrence of lobar or segmental atelectasis does not of itself warrant the interruption of the course of an A.P. Adequate material is therefore available at this institution for the numerical examination of the prognostic effects of such atelectasis.

Data

Data for this investigation were obtained from consecutive cases of A.P. induced at the Cheshire Joint Sanatorium between early 1935 and the end of 1945. That all these cases were finally complete was shown by thorascopic examination as well as by *x*-ray films. In all cases sputum was either negative throughout or converted to negative by effect of the A.P.

The collecting of data from earlier sanatorium cases has the advantage of allowing a long period of follow-up—of five years in all cases and of ten years in about half of them. Also, in earlier years case selection for therapeutic pneumothorax, and the subsequent management, were less informed than at the present day. We are thus able to collect for assessment groups of cases which would not be seen in current practice, such as those in which there is a persistent cavity in an anatomically complete A.P. One disadvantage of collecting data from earlier cases is the absence of information from routine bronchoscopic examinations.

Where disease in the contralateral lung was regarded as a possible factor in life prognosis the case was excluded—for instance, if on the contralateral side there was an incomplete A.P., or if an attempt at induction of an A.P. had failed on the contralateral side. With regard to contralateral disease, the cases included had (*a*) no radiological evidence of disease; (*b*) disease controlled by an uncontroversial A.P.; or (*c*) disease of moderate extent, healing, and not sufficient to warrant active intervention and not producing a positive sputum.

Disease in the pneumothorax lung, as it appeared prior to A.P. induction, was classified according to its type and its extent.

The type of disease was dealt with under three headings. (1) Cavitated disease: the cavity was at least 5 cm. in diameter, or multiple cavities had a total diameter of at least 5 cm. (2) Exudative disease: the disease was predominantly of a type with a confluent and ground-glass radiographic appearance. (3) Productive disease: cases not classified under (1) or (2) appeared under this heading, so that a variety of radiographic appearances of tuberculous infiltration are included.

The extent of the disease was classified according to the total number of zones in the P.A. *x*-ray film of the chest which showed infiltration of tuberculous infection. The zones are demarcated by two horizontal lines passing through the second and fourth costal cartilages, thus dividing each lung field into three zones. This classification of disease extent was used by Hartley *et al.* (1935).

Atelectasis is recorded only if it persisted for three months or more. Transient atelectasis following thoracoscopy (Hess, 1951; Penman and Miller, 1952) is thus excluded. In regard to the extent of atelectasis, the cases were classified into four groups—total, lobar, segmental, and nil. Lobar atelectasis includes that of an upper or a lower lobe, there being

no case of a solitary middle-lobe atelectasis. Segmental atelectasis includes cases in which a recognizable segment is collapsed, but cases with more than one atelectatic segment are also included under this heading.

Pleural effusions were recorded only if they were large enough to cover the diaphragm, and if persistent enough to require aspiration. Small or transient effusions are thus excluded. A proportion of these effusions occurred in the later course of the artificial pneumothorax, and some of the data of this complication were obtained from a questionary sent to the chest physicians of clinics. Details of survival and duration of the pneumothorax were also available from this source.

Data concerning the occurrence of contralateral spreads, and the activity of disease in the pneumothorax lung, or the degree of re-expansion of the pneumothorax lung after termination of the A.P., were less readily obtained. This part of the investigation entailed use of records and *x*-ray films at many clinics, and in some cases these records were inadequate for the purpose. For this and other reasons, only 159 cases of the original 266 were available for this part of the inquiry.

Results are tabulated and analysed according to the four groups of atelectasis, and are considered under the following headings: pleural effusions; re-expansion of the A.P. lung, and re-aeration of the atelectatic area; reactivation of disease in the A.P. lung at the termination of pneumothorax; contralateral spread of disease; and mortality rates.

Pleural Effusions

As already stated, only persistent effusions are recorded. They are classified according to whether purulent or non-purulent and according to culture reports into T.B.-negative effusions, T.B.-positive effusions, and empyemata. All the empyemata were positive for the tubercle bacillus. As in the tables below, it is usually convenient to group all three types of effusion together as "persistent effusions," and the last two types together under the heading of "all positive effusions."

A comparatively high death rate has been associated with groups of A.P. cases having persistent pleural effusions (Edwards *et al.*, 1944; Morriss, 1942). Brock *et al.* (1937) believe that in such cases of pleural effusion the active disease in the underlying lung is the detrimental factor rather than the effusion itself. In considering the subject of the prognosis of atelectasis, however, it is obviously important to note any association between atelectasis and pleural effusion.

Houghton (1950) believes atelectasis in the A.P. to be a direct causative factor of T.B.-positive effusions. In his own words, "atelectasis of a grossly diseased lobe with or without cavitation will be followed almost inevitably by pleural effusion, tubercle bacilli will appear in the fluid and sooner or later an empyema will develop." In support of this view he quotes 50 consecutive A.P. cases in which tubercle bacilli had been demonstrated in the pleural fluid—many cases were empyemic. In 86% of these 50 cases a black lobe or lung was prominent in the *x*-ray picture. A corresponding group of T.B.-negative effusions did not show such atelectasis, or showed it only as a transitory phenomenon.

In Table I the occurrence of effusions among the cases of the present investigation is shown. The cases having a persistent cavity in the pneumothorax lung are dealt with separately, and effusions of the three types are shown in relation to the extent of atelectasis. Of the 28 cases with T.B.-positive and the 20 cases with T.B.-negative effusions, 25 (90%) and 12 (60%) respectively had some degree of atelectasis. The former finding is similar to the one quoted from Houghton. However, there seems good reason to analyse the matter further before accepting the view that atelectasis is the causative factor of such pleural effusions.

First of all, the persistent cavity group, which includes atelectatic and non-atelectatic cases, has a significantly higher incidence of effusions than the group of cases without persistent cavitation (Table II).

TABLE II.—*Persistence of Cavitation and Effusion Incidence*

Cases	No.	T.B.-positive Effusions	All Persistent Effusions
Persistent cavity ..	20	8 (40%)	9 (45%)
No persistent cavity ..	246	20 (8·1%)	39 (15·8%)
Difference		31·9%±11%	29·2%±11%

It is therefore justifiable to omit for the time being the cases with persistent cavitation and inspect the incidence of effusion in the remaining cases. Among the latter it is seen (Table III) that a positive correlation exists between incidence of persistent effusions or of T.B.-positive effusions, and extent of atelectasis. A similar correlation is observed between extent of disease by zones in the A.P. lung and the incidence of persistent or T.B.-positive effusions (Table IV).

TABLE III.—*Atelectasis and Effusion Incidence (Persistent Cavity Cases Omitted)*

Atelectasis	No.	T.B.-positive Effusions	All Persistent Effusions
Total	13	4 (31%)	7 (54%)
Lobar	44	8 (18%)	12 (27%)
Segmental	102	6 (6%)	11 (10·8%)
Nil	87	2 (2·3%)	9 (10·3%)
	246	20 (8·1%)	39 (15·8%)
	χ^2:	p<0·01	p<0·01

TABLE IV.—*Extent of Homolateral Disease and Effusion Incidence (Persistent Cavity Cases Omitted)*

Zones of Disease	No.	T.B.-positive Effusions	All Persistent Effusions
1	45	0	1 (2·2%)
2	154	9 (5·8%)	22 (14·2%)
3	47	11 (42·6%)	16 (34%)
	246	20 (8·1%)	39 (15·8%)
	χ^2:	p<0·01	p<0·01

On the other hand, between the type of initial disease in the pneumothorax lung and the incidence of pleural effusions there is little or no correlation. Indeed, the differences of incidence of effusion among the three types of disease (Table V) are no greater than could occur by chance.

TABLE V.—*Type of Homolateral Disease and Effusion Incidence (Persistent Cavity Cases Omitted)*

Type of Disease	No.	T.B.-positive Effusions	All Persistent Effusions
Cavitated	85	8 (9·4%)	17 (20%)
Exudative	36	5 (14%)	7 (19·5%)
Productive	125	7 (5·6%)	15 (12%)
	246	20 (8·1%)	39 (15·8%)
	χ^2	p=0·25	p=0.25

TABLE I.—*Effusions and Atelectasis*

Atelectasis	No.	T.B.-negative Effusions	Non-purulent T.B.-positive Effusions	Empyemata
Persistent Cavity Cases				
Total	1	—	—	—
Lobar	8	—	3	1
Segmental ..	6	—	1	2
Nil	5	1	1	—
	20	1	5	3
Non-cavity Cases				
Total	13	3	4	—
Lobar	44	4	6	2
Segmental ..	102	5	3	3
Nil	87	7	2	—
	246	19	15	5

It should be noted that the χ^2 test quoted in the tables above does not measure the strength of an association or indicate whether or not a correlation is statistically significant. It serves to show, however, where differences are no greater than might occur by chance.

The findings in Table V seem to disagree with the views of Rafferty (1947), who states that there is a higher incidence of pleural effusions where the pneumothorax lung originally showed pneumonic tuberculosis or giant cavitation.

The extent of the initial disease and the extent of atelectasis are both correlated with the incidence of pleural effusions. That the first-named two variables are themselves associated is demonstrated in Table VI. The question therefore arises, Which of the two variables is primarily associated with the occurrence of pleural effusion?

TABLE VI.—*Distribution of Extent of Disease and of Atelectasis (Persistent Cavity Cases Omitted)*

Atelectasis Extent	One Zone Infiltrated	Two Zones Infiltrated	Three Zones Infiltrated
Total	0	4	9
Lobar	1	28	15
Segmental ..	16	71	15
Nil	28	51	8
	45	154	47

It should be possible to deduce the answer, given sufficient cases. The cases under consideration should be grouped according to the extent of atelectasis, and each such group should be examined to find if the incidence of effusion is still proportional to the extent of the disease by zones and vice versa. With the present number of cases the best that can be done is to analyse the subgroups containing the greatest numbers—that is, "segmental atelectasis" (Table VII) and "two zones of disease" (Table VIII)—for the incidence of persistent effusions.

TABLE VII.—*Incidence of Effusion Related to Extent of Disease (Cases with Segmental Atelectasis Only)*

	Extent of Disease in Zones			
	1	2	3	Total
Incidence of persistent effusions	0 (16)	8·5% (71)	33·3% (15)	10·8% (102)
	χ^2: $p<0.01$			

Table VII demonstrates a positive correlation between effusion incidence and extent of disease, but in Table VIII (with a larger number of cases included) there seems to be no association between effusion incidence and degree of

TABLE VIII.—*Incidence of Effusion Related to Degree of Atelectasis (154 Cases with Two Zones of Disease Only)*

	Degree of Atelectasis				Total Incidence
	Nil	Segmental	Lobar	Total	
Incidence of persistent effusions	15·7% (51)	8·5% (71)	21·4% (28)	50% (4)	14·3% (154)

atelectasis. This analysis, so far as it goes, suggests that extent of initial disease in the pneumothorax lung is the primary factor in the causation of effusions rather than atelectasis *per se*.

It should be remembered that the classification of the extent of disease in a lung according to the number of zones seen to be infiltrated in a P.A. *x*-ray film is not an exact method. No allowance is made for the density of involvement of each zone.

Cuthbert and Nagley's (1948) description of the radiological "black lobe" when it is seen at thoracoscopy is of a mixture of collapsed and aerating tissue. The pathological finding associated with this *x*-ray appearance was of multiple small foci of parenchymal and bronchiolar infection. To produce the homogeneous radiological appearance of the "atelectatic" lobe or segment, such an infiltration would be expected to be dense in character within the related lobe or segment.

Erwin (1939) notes that lobes which collapse in an A.P. and fail to expand early are extensively diseased ones; and Morland and Price Thomas (1952) state that when atelectasis appears in an A.P. the lobe or segment so affected is usually the part of the lung most seriously diseased.

The extent of the disease as seen in a P.A. film is one factor in the incidence of pleural effusions, and it is logical to assume that the density of infiltration might also contribute to its causation. Both extent and density of infiltration are apparently associated with the occurrence of atelectasis in a pneumothorax. An incidence of effusions in proportion to the extent of atelectasis in the A.P. (Maher-Loughnan, 1950; Farquharson, 1951) may well be accounted for by the extent and density of parenchymatous infiltration initially present in the lung.

Re-expansion of the Pneumothorax Lung

Re-expansion of the pneumothorax lung was noted from its radiological appearance at least one year after cessation of refills. The appearance of the lung and also of the adjacent structures—diaphragm, chest wall, and mediastinal organs—was then observed. Cases were classified into three groups. (1) Full re-expansion. The lung appeared expanded and normal apart from healed disease; no atelectasis was apparent; and there was no displacement of adjacent structures. (2) Incomplete re-expansion. This group included cases in which the lung itself was not fully expanded—commonly an apical space remained. Also included are a few cases in which the lung was expanded except for a persistent atelectatic lobe or segment. Cases in which the lung seemed to be expanded but in which moderate displacement of the mediastinum or other chest structures occurred also appear in this group. (3) Unexpandable lung. In this group either the lung failed appreciably to re-expand and a dead space remained or there was gross displacement of mediastinal structures and contraction of the chest wall and diaphragm.

Of the original 20 in the persistent cavity group and the 246 in the non-cavity group, only 3 of the former and 156 of the latter are available by which to assess re-expansion. These are the numbers of cases which can be followed up radiologically until at least one year after termination of the pneumothorax. Of the 246 cases, 90 are thus excluded for various reasons—A.P.s not abandoned at the time of assessment, adequate records not available, patients moved to inaccessible areas, etc. That the 156 cases are, practically speaking, an "unselected" sample of the original consecutive group of cases is, however, indicated by the fact that the incidence of mortality and of pleural effusion occurs at approximately the same rates as in the original group of 246.

Only six cases which left the sanatorium with a total atelectasis and only three that were discharged with persistent cavitation in the A.P. have been followed up. There was no case with a full re-expansion among these nine, and it is thought reasonable to consider them separately from the main group of 150 cases.

Among these 150 cases a full re-expansion of the A.P. lung occurred in approximately half, while an unexpandable lung was seen in 10%. The distribution of expansion in relation to atelectasis is seen in Table IX.

TABLE IX.—*Re-expansion and Atelectasis (Persistent Cavity and Total Atelectasis Cases Excluded)*

Atelectasis	Total	Full Re-expansion	Partial Re-expansion	No Re-expansion
Lobar	33	15 (45%)	15	3 (9%)
Segmental ..	63	31 (50%)	23	9 (14%)
Nil	54	32 (63%)	19	3 (6%)
	150	78	57	15

Table IX shows that a diminished proportion of full re-expansion occurs in relation to the extent of atelectasis. On the other hand, atelectasis is not associated with unexpandable lung.

TABLE X.—*Re-expansion According to Effusion Present (Persistent Cavity and Total Atelectasis Cases Excluded)*

Pleural Effusion	Total Cases	Full Re-expansion	No Re-expansion
T.B.-positive ..	12	1 (8%)	5 (42%)
T.B.-negative ..	11	4 (36%)	2 (18%)
No effusion ..	127	73 (57%)	8 (6%)
	150	78	15
	χ^2:	p<0·01	p<0·01

Two factors which could be expected to restrict the proportion of cases showing full re-expansion in a group of atelectasis cases (Jackson, 1952), as compared with a group with no atelectasis, are: (*a*) persistence of atelectatic lobe or segment; and (*b*) a higher incidence of pleural effusions which accompany (though, as previously reasoned, are not caused by) atelectasis.

A lower incidence of full re-expansion among cases having effusions, particularly effusions positive for tubercle bacilli, is shown in Table X.

The importance of effusion, especially empyemata, in hindering lung re-expansion is well known, and has been mentioned, among others, by Mitchell (1951) and Heaton and Ogden (1950).

Persistence of an atelectatic lobe was seen in only two of the 150 cases and of an atelectatic segment in only four cases. So that persistent atelectasis is not here a factor of any great importance in limiting the proportion of cases having a full re-expansion. Incidentally these six cases were not associated with any untoward final result. Erwin (1939) reports that the few lobes which fail to re-expand are always extensively diseased, and permanent atelectasis is to be regarded as a selective collapse maintained automatically; this coincides with my own impression of these six cases.

The duration of the pneumothorax has been shown (Heaton and Ogden, 1950; Mitchell, 1951) to influence pleural thickening, and therefore lung re-expansion. It is worthy of note that 11 out of the 15 cases of unexpandable lung had had an A.P. for over six years. In fact, all of the unexpandable lung cases had either an over-prolonged A.P. or a T.B.-positive pleural effusion, or both. This suggests that pleural thickening is the cause of this undesirable sequel—which is the view of Rafferty (1947)—rather than a possible bronchial factor (Farber, 1942; Mitchell, 1951).

Duration of the A.P. in the cases of this investigation has a "chance distribution," being largely dependent upon the preference of the various physicians working at 15 different clinics.

It may be that a bronchial factor limits re-expansion in the total-atelectasis group, for in four out of six such cases followed up a persisting partial atelectasis was the reason for failure of full expansion. The other two cases exhibited an unexpandable lung. Of the persistent-cavity group only three cases were followed up completely, and these showed partial re-expansion.

Groups of cases with lobar or segmental atelectasis (with no persistent cavitation) may therefore be expected to have a smaller proportion of cases exhibiting a complete re-expansion. This is chiefly on account of the incidence of pleural effusions in such groups. It has already been reasoned that the extent and density of the original lung disease, and not the atelectasis itself, is the underlying factor in effusion incidence.

Reactivation of Disease

The occurrence of active tuberculous disease in the re-expanded pneumothorax lung was investigated in the 156 cases without persistent cavitation which were followed up until one year after the termination of pneumothorax. Activity of disease was determined by sputum reports and other clinical evidence, as well as by the radiological appearance of the re-expanded lung. Three out of the six cases with total atelectasis showed reactivation. The remaining 150 cases are grouped separately, and in Table XI the incidence of reactivation is shown according to the duration in years of the pneumothorax. It is apparent that the incidence of reactivation in these cases is independent of A.P. duration if those of under one year are first excluded. For this reason, in examining the incidence of reactivation in relation to lobar and segmental atelectasis, cases in which the A.P. is of longer duration than one year are grouped together (Table XII). It is apparent that there is no association between lobar and segmental atelectasis and the incidence of reactivation.

TABLE XI.—*Reactivation and A.P. Duration (Total Atelectasis Cases Excluded)*

A.P. Duration	Cases	Reactivation Cases
Less than 1 year	5	4 (80%)
1 to 2 years	16	1 (6·2%)
2 to 3 „	14	1 (7·3%)
3 or more years	115	9 (7·8%)

TABLE XII.—*Incidence of Reactivation According to Atelectasis (Total Atelectasis Cases and Cases with A.P. Duration Under One Year Excluded)*

Atelectasis	Cases	Cases with Reactivation
Lobar	32	3 (9%)
Segmental	60	4 (6·6%)
Nil	53	4 (7·5%)
	145	11 (7·6%)

It is worth noting that the total incidence of reactivation is of the same order as that found by some other observers of A.P. series—Potter (1942) gives 7½%, Morriss (1942) 6%, Aycock and Keller (1942) 5½%, and Hurst and Schwartz (1942) 10%.

In the persistent-cavity group there is insufficient data for consideration from the point of view of reactivation or of contralateral spread of disease.

Contralateral Spread

The occurrence of a bronchogenic spread of disease into the contralateral lung in A.P. cases is given a varying incidence by different observers. Potter (1942), for instance, noted an incidence of 6%, while Morriss (1942) found it in 30% of his cases. In the present 156 cases, followed up in detail, the total incidence seems to be 12%. How this is distributed in relation to atelectasis is shown in Table XIII.

TABLE XIII.—*Incidence of Contralateral Spread and Atelectasis*

Atelectasis	Total Cases	Cases with Spreads
Total	6	2 (33%)
Lobar	34	2 (6%)
Segmental	62	9 (14·5%)
Nil	54	5 (9%)
	156	18 (11·5%)

With the possible exception of the cases with total atelectasis, the number of which is too small for assessment, the incidence of contralateral spread is not associated with atelectasis (Table XIII).

Mortality Rates

Cedric Shaw (1933) discusses prognosis in artificial pneumothorax cases and says, "The one real ponderable in pulmonary tuberculosis is mortality." But to each death from tuberculosis, sociological and immunological as well as clinical factors make their contribution. Deductions therefore cannot be made from differences in mortality rates

between one group of tuberculous subjects and another unless such differences are obvious and significant. In Table XIV such a significant difference in mortality rates is seen when the cases with and without persistent cavitation are compared.

TABLE XIV.—*Mortality Rates in Relation to Persistence of Cavitation*

Cases	No. at Risk, 5 Years	Dead at 5 Years	No. at Risk, 10 Years	Dead at 10 Years
Persistent cavity ..	20	8 (40%)	13	11 (85%)
No persistent cavity	246	13 (5·25%)	122	19 (15·6%)
Difference ..		34·75%±11%		69·4%±11%

Farquharson's (1951) results of survival among A.P. cases with atelectasis are in accordance with those of Table XIV. Of 25 cases with cavitated and 75 cases with non-cavitated atelectasis, she reports 19 (76%) and 13 (17.3%) respectively as ill or dead. Also, among the good A.P. cases in the series of Foster-Carter *et al.* (1952) 7 out of 10 with persistent cavitation died within eight years.

In non-cavitated atelectatic cases, evidence of a mortality rate in relation to the extent of atelectasis might well be expected. The association between the extent of atelectasis and that of disease by zones has already been demonstrated (Table VI); and a remarkable correlation between life expectation and disease extent by zones has been demonstrated by Hartley *et al.* (1935) and more recently by Foster-Carter *et al.* (1952). The latter investigators show that the law "Expectation of survival in pulmonary tuberculosis varies inversely as the radiological extent of the disease" applies equally to groups of collapse or non-collapse cases.

In fact, there seems to be a slight trend of association between extent of atelectasis and mortality rates (Table XV). So small a trend, however, argues against atelectasis *per se* being a factor in life prognosis, having regard to the influential factor of disease extent by zones.

TABLE XV.—*Mortality Rates in Relation to Atelectasis (Persistent Cavity Cases Omitted)*

	Atelectasis			
	Total	Lobar	Segmental	Nil
Dead in 5 years..	15·4% (13)	6·8% (44)	5·9% (102)	2·3% (87)
„ „ 10 „ ..	28·6% (7)	18·5% (27)	14·3% (49)	12·8% (39)

The figures in parentheses show the number of cases followed up.

Foster-Carter *et al.* also note the mortality in 45 of their A.P. cases with lobar or segmental atelectasis but no persistent cavitation. The survival rate in this group was exactly the same as that of the group of A.P.s as a whole.

Discussion

In the group of cases having persistent cavitation in the pneumothorax lung, the comparatively high rates of death and incidence of pleural effusions are striking. It is instructive to note that these mortality and effusion rates are quite similar to those reported in some series of pneumothoraces in which there was demonstrable endobronchial tuberculosis (Chamberlain and Gordon, 1942; Tuttle *et al.*, 1942; Rafferty and Shields, 1943). Most of the cases of the present investigation were treated before routine bronchoscopy became available, but these findings suggest that where there is persistent cavitation in a pneumothorax lung there is concomitant endobronchial tuberculosis.

On the other hand, in the group without persistent cavitation, judging by the course and prognosis, the presence of lobar or segmental atelectasis would not appear to indicate an underlying endobronchial disease. The prognosis regarding life and the occurrence of effusions, as well as the incidence of contralateral spread and ipsilateral reactivation of disease, are no worse than among cases with no atelectasis.

The small number of cases with total atelectasis, however, seem to share the grave prognosis of the persistent-cavity group.

As a result of the work of Coryllos (1933) atelectasis in adult pulmonary tuberculosis was for a long period believed to be synonymous with endobronchial tuberculosis (Pinner, 1945). More recently, alternative mechanisms of lobar and segmental atelectasis have been described—for example, by Cuthbert and Nagley (1948) and Coello and Nagley (1948). According to these writers the aetiology of atelectasis (as defined in the present investigation) can lie peripheral to the major bronchi. Moreover, observance of the recognized tenets in prescribing A.P. therapy, such as withholding it in the presence of "hot" disease, of a "wheeze," or of a tension cavity, will serve to avoid many cases in which tuberculous bronchitis might be present. The fact of sputum conversion by the A.P. also serves to exclude from this series cases of endobronchial tuberculosis (Davies, 1943).

Lobar and segmental atelectasis may thus be observed radiologically in the pneumothorax lung in the absence of endobronchial tuberculosis, and in such cases its occurrence seems to be a benign circumstance.

Summary

Consecutive anatomically complete A.P. cases with sputum conversion were followed up for at least five years. They were grouped according to the presence of persistent cavitation (20 cases) and, in those without persistent cavitation (246 cases), according to the presence of total, lobar, segmental, or no atelectasis in the A.P. lung.

Cases with persistent cavitation showed significantly higher mortality rates and incidence of pleural effusions than the remaining group.

Cases without persistent cavitation showed an incidence of pleural effusion which was in proportion to the extent of atelectasis. There is evidence, however, that this was because of the concomitant extent of initial disease in the pneumothorax lung rather than a result of atelectasis *per se*.

In 156 of the cases without persistent cavitation it was possible to evaluate the incidence of contralateral spreads, of disease reactivation in the A.P. lung, and the completeness of re-expansion after termination of the A.P.

The great majority of atelectatic lobes and segments (excluding cases with total atelectasis) re-aerated at the termination of the A.P. Full re-expansion depended largely on whether or not pleural effusion had been present.

If cases with total atelectasis are excluded there was no connexion between the presence of atelectasis and the occurrence of contralateral spreads or the occurrence of disease reactivation in the A.P. lung.

Mortality rates in the group with no persistent cavitation showed no significant relationship with the occurrence of lobar or segmental atelectasis.

In the light of these findings, alternative aetiologies of atelectasis in a pneumothorax lung are discussed.

It is concluded that the occurrence of persistent cavitation or of total atelectasis in an A.P. lung carries a grave prognosis. The occurrence of lobar or segmental atelectasis, however, does not, of itself, appear to worsen prognosis.

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FATAL CASE OF MARROW APLASIA AFTER TREATMENT WITH CARBIMAZOLE

THE EFFECT OF A.C.T.H.

BY

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Carbimazole (" neo-mercazole "; 2-carbethoxythio-1-methylglyoxaline) must now be added to the long list of drugs that may cause marrow aplasia with depression of all the blood-forming elements.

The incidence of marrow depression due to antithyroid drugs is relatively low and is still decreasing as less toxic preparations become available. A report on the treatment of 150 patients with carbimazole by Doniach (1953) stresses the absence of any toxic effects in her cases, and only mild toxic reactions were found to follow treatment of 14 patients with this drug by Lawson and Barry (1951). Poate (1953), in a survey of nine cases, states that carbimazole in therapeutic doses does not interfere with the leucocytes. In a recent study on the clinical effects and toxic reactions of carbimazole, Bartels (1953) found that 3 of his 52 patients treated with this drug developed toxic manifestations. Two of these were skin reactions, the third had agranulocytosis, which however, cleared up within 14 days after discontinuation of the drug.

Rosenbaum and Reveno (1953) reported a case of agranulocytosis and toxic hepatitis secondary to methimazole (" mercazole "), the forerunner of carbimazole, and referred to two instances of agranulocytosis due to this drug (Croke and Berry, 1952; Specht and Boehme, 1952). In the experience of Davidson (1953), who discusses the use of methimazole in 44 patients, this drug is definitely less toxic than methylthiouracil, and, although slightly more toxic than propylthiouracil, the incidence of severe toxic reactions is of the same order of magnitude as with the latter drug. The overall incidence of toxic reactions with methimazole is given by various workers as 4.5–6%, that of agranulocytosis as 0.15%.

The following case is, we believe, the first example of a fatal marrow aplasia following the use of carbimazole.

Clinical History

A married woman aged 23 was admitted to hospital on June 8, 1953, suffering from severe thyrotoxicosis. Her B.M.R. was 74%. As she had suffered from extensive bilateral bronchiectasis for several years, surgical treatment for her thyrotoxicosis was considered undesirable, and she was put on carbimazole, 10 mg. three times a day, on June 19. She was discharged from hospital a fortnight later and continued as an out-patient with carbimazole in the same dosage as her sole medication. When seen a month after discharge her thyrotoxicosis was under control and she felt much better.

On August 12, just under eight weeks after beginning carbimazole she noticed red patches on her skin and was coughing up more blood from her bronchiectatic cavities than ever before. The drug was discontinued and she was admitted to hospital. Purpuric haemorrhages were found over most of her body and on her mucous membranes. There was no soreness of her throat, but she had a pyrexia of between 101 and 103° F. (38.3 and 39.4° C.). Hess's test was strongly positive. A blood count on the day of admission showed: haemoglobin, 64%; red cells, 4,110,000; white cells, 4,000, with a normal differential count; platelets, 61,000; bleeding and clotting times, normal.

Four days later her haemoglobin had fallen to 54%, her white count to 1,000 cells with 29% polymorphs, and her platelets to 25,000. She was transfused with 2 pints (1,140 ml.) of fresh blood. Her bone marrow taken at this time showed marked agranulocytosis and only one megakaryocyte in three films. Electrophoretic examination of the serum, both before and after the first transfusion, failed to reveal the presence of any α_2-globulin such as may be present in certain cases of purpura (Bernfeld and Stefanini, 1951).

Treatment directed to the control of infection consisted of penicillin for one week, which was then replaced by aureomycin, 500 mg. six-hourly, and this was continued throughout the rest of her illness. She was given approximately 2 pints (1,140 ml.) of fresh blood at weekly intervals for the next eight weeks.

Cortisone was begun on August 23, 11 days after the onset of purpura, the initial dose being 100 mg. six-hourly, followed on the next and subsequent days by 50 mg. six-hourly. As she made no detectable response the cortisone was replaced by adrenocorticotrophic hormone (A.C.T.H.) with a dosage of 40 mg. six-hourly. After starting cortisone the patient's condition was reasonably satisfactory and her temperature settled on aureomycin, but she continued to get crops of petechiae, although Hess's test had become negative before cortisone was started. Her blood picture, which was examined daily, remained unchanged. The platelets were virtually absent, her haemoglobin was maintained in the region of 50% with transfusions, and her white cells remained round about 1,000, with 20 to 30% polymorphs.

This state of affairs continued for 17 days, during which time the dose of A.C.T.H. was gradually reduced from 40 mg. six-hourly to 15 mg. twice daily, as supplies were running out. Her temperature rose to 101° F. (38.3° C.) and she had a haemoptysis of 12 oz. (340 ml.). A fresh supply of A.C.T.H. was obtained and her condition improved, but the drug was running short by October 3, and was tailed off and discontinued on October 7. Three days later her temperature, which had been rising, reached 102° F. (38.9° C.); she had a haemoptysis of 16 oz. (450 ml.), and several smaller ones. Her condition became critical. Her pulse rate rose to 140 a minute, and her blood pressure fell from its normal level of 130/80 to 90/50. The bleeding from her lungs was stopped by two transfusions of 2 pints and 1 pint (1,140 and 570 ml.) of blood respectively, but she remained desperately ill.

The next day A.C.T.H. was again obtained and 30 mg. was given intramuscularly with a further pint (570 ml.) of fresh blood. Two hours later her general condition was better, her colour improved, and her pyrexia began to settle. The A.C.T.H. was continued in doses of 15 mg. six-hourly, and a week later, on October 19, her blood count showed the first sign of improvement; haemoglobin, 72%; red cells, 3,890,000; white cells, 3,000 (60% polymorphs); 60 nucleated red cells per c.mm.; platelets 10,000.

The figures of her blood count remained round about the same level and on November 6 A.C.T.H. was stopped. On this occasion after withdrawal of A.C.T.H. her temperature did not rise or her condition deteriorate and her blood count had remained substantially the same, although transfusions of 2 pints (1,140 ml.) were required every two to three weeks instead of weekly. Her bone marrow on November 9 appeared completely aplastic, but the drop in cells was mainly in the red-cell series, her white blood count being constant at 2,000–3,000 and her platelets 10,000–50,000 per c.mm. Her condition appeared to improve for a time, but remained precarious throughout. The haemorrhagic incidents became more frequent. She was admitted for a further transfusion, developed a cerebral haemorrhage, and died before any effect of a new supply of cortisone could take place. She died on December 28—that is, 139 days after the onset of her blood disorder.

Post-mortem examination revealed a pale and fatty bone marrow, the presence of petechial haemorrhages in most organs, and a cerebral haemorrhage on the right side. Bronchiectasis, fatty degeneration of the liver, and deposition of haemosiderin in the liver and spleen were found. No significant histological changes were present in the endocrine organs.

Discussion

It is the experience of several workers that marrow function usually returns spontaneously in about a week after discontinuing the offending drug (Hutt and Lee, 1953). We felt at first that both cortisone and A.C.T.H. were of no value in the management of this case, but, as the aplastic condition of her marrow persisted and she did not deteriorate clinically, we began to think that it might be having a life-saving effect. Coincidentally with the reduction in the dose of A.C.T.H. to an ineffective level she developed on two occasions a pyrexia and severe haemoptysis, and on the second was desperately ill. On both occasions when an effective dose of A.C.T.H. was restarted her general condition improved in a matter of hours.

We found no evidence that cortisone and A.C.T.H. had any effect in hastening recovery of normal marrow function. Sternal marrow puncture was not used throughout as a guide to the amount of regeneration, as daily blood counts showed no signs of recovery and the patient was having to endure many but inevitable needle pricks and discomforts. We felt, however, that we were giving cortisone and A.C.T.H. a proper trial, as they were not begun until 11 days after the onset of purpura and the discontinuation of carbimazole. We suggest that these drugs would have produced signs of regeneration of the marrow after a course lasting 72 days if they were capable of bringing about such an effect.

Summary

A fatal case of marrow aplasia secondary to carbimazole is reported. It is believed that this is the first recorded example due to this drug.

Cortisone and A.C.T.H. were given for 72 days, and on two occasions when the dose was reduced the patient immediately became extremely ill with pyrexia and haemoptysis. A third attempt at withdrawal of the drug was achieved without untoward effects, but only after the peripheral blood picture had shown some improvement over a period of 18 days.

It is believed that cortisone and A.C.T.H. kept this patient alive while they were being administered, but no evidence was found that either of them assisted in the regeneration of the marrow.

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PRURITUS AND ITS MANAGEMENT*

BY

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Pruritus implies the peculiar uncomfortable sensation of itching, which leads to the physical response of scratching but is not associated with any inflammatory changes of the skin. As with love, it is difficult to know where it is bred, in the skin or in the head; whether in the nerve endings or in the accelerated appreciation of the sensation. It may even originate in the cerebral cortex.

Whether one itches may depend on the degree of attention paid to somatic sensation. We know that if we are obliged to keep still at attention, within a few minutes an intolerable itch is likely to develop, often near one of the orifices.

Itching is very easily suggested. The sight of a head infested with crawling lice will induce in the novice a crawling itching feeling over the skin, which might even be localized to the same area.

The pleasurable element of itching is a matter of common experience. According to Jowett, Socrates dilates in his dialogues on the sensual pleasure of itching and scratching. The back scratcher of the Chinese, so finely carved in the shape of a hand or a claw, indicates the artistic appreciation of the instrument and equally the pleasure it gives when used.

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Allergic Reactions

The peripheral nerve endings are stimulated by the histamine-like and other substances (Feldberg, 1953) produced by allergic reactions. Itching also occurs as a manifestation of physical allergy to heat, cold, and friction. Allergy to roundworms and threadworms can occasionally lead to general itchiness as well as to anal and vulval pruritus. Allergies to foods may be responsible for a generalized or localized pruritus as a manifestation of a specific sensitivity. The itching over the face and elsewhere felt after the consumption of beverages is associated with reflex vasodilatation and may be cholinergic.

Pruritus is an early and valuable warning sign of allergy or of intolerance to many drugs—for example, to heavy metals, mepacrine. Other drugs, such as cocaine, owing to their cerebral action, may give rise to hallucinations of tiny living animals under the skin.

Diabetes and chronic renal insufficiency may present first as a pruritus. The fact that no instance of these diseases was noted in the series of 64 consecutive cases of pruritus (Table I) is no indication of the relative frequency of their occurrence, for the urinary findings lead the diabetic and nephritic patient to the general physician.

TABLE I.—*Age Distribution of 64 Consecutive Cases of Generalized Pruritus Without Physical Signs, and the Significant Associations*

Age	No. of Cases	Associations	
0–19	2	Mother with anxiety state—overtreated	1 case
		Allergic, hay-fever, and asthma	1 ,,
20–39	15	Xerodermia (congenital) and cold	2 cases
		Xerodermia (congenital)	1 case
		Hodgkin's disease	1 ,,
		Pregnancy	3 cases
		Drug: atropine, codeine	1 case
		Cardiac insufficiency (severe mitral stenosis)	2 cases
		Obsessive	2 ,,
		Anxiety state	2 ,,
		Parasitophobia	1 case
40–59	13	Anaemia	1 case
		Cardiac insufficiency	2 cases
		Acquired xerodermia	1 case
		,, ,, ? thyroid insufficiency	1 ,,
		Anxiety	2 cases
		Depression—testicular atrophy	1 case
		Manic depressive	1 ,,
		Menopausal depression	1 ,,
		Parasitophobia	1 ,,
		Undetermined	2 cases
60–74	34	Anaemia	1 ,,
		Hypertension	3 cases
		Xerodermia (1 with anaemia, 1 with hypertension)	5 ,,
		Deficiency (gastrectomy)	1 case
		Cardiac insufficiency (right-sided)	1 ,,
		Cardiac insufficiency	3 cases
		Carcinoma—bronchus	1 case
		Reticulosarcoma	1 ,,
		Delusional	1 ,,
		Obsessional	10 cases
		Anxiety state	1 case

It will be noted in Table I that a congenital or acquired dry skin, a deficiency of iron, circulatory insufficiency, psychoneurotic or psychotic mental disorders, and malignancy occur in the age groups above 20 years.

The Deficiency Group

The nutritional disorders due to deficiencies of iron, vitamin A, vitamin-B_2 group, vitamin C, and other essential elements may lead to a loose hyperkeratosis, with a degree of atrophy causing discomfort, and an itching skin.

The associated diminution of sweat and sebum, with their emollient and plasticizing constituents, will also encourage the exposure of terminal nerve endings within the epidermis. Cold weather and friction of clothing will the more readily provoke the sensation of itching under these circumstances, and this also applies to the dry thin skin of old age (see Table II).

TABLE II.—*Incidence of Dry Skin, Cardiac Insufficiency, and Hypertension*

Age	No. of Cases	Dry Skin	Cardiac Insufficiency	Hypertension
20–39	15	3	2	
40–59	13	2	2	
60–74	34	5	4	7

An example of this deficiency group was the case of a woman aged 43 with a three-years history of generalized itching and a haemoglobin of 45%. When the anaemia was successfully treated with iron and vitamin C her pruritus improved.

The menopause in both sexes may be associated with an itchy skin. In the female the itching and flushing occur together, and the itching is due either to alteration of the skin tension or to increased production of choline-like substances in the skin. The work of Grant *et al.* (1936) suggests that an undue sensitivity or reactivity to acetylcholine occurs in heat and exercise urticaria, and pruritus may be the first and only symptom of this sensitivity.

The alleviation of the itching by the administration of testosterone and/or oestrogen would, I believe, be more readily ascribed to a central effect, for the result of treatment is so rapid. However, testosterone is known to increase by as much as 50% the amount of oxygenated blood in the skin, and the effect of this on enzymic activity and nutrition of the skin is readily appreciated.

The skin may become anoxaemic as a result of circulatory insufficiency, and this may lead to pruritus.

Two examples of severe itching with much excoriation in young adults with well-developed mitral stenosis were observed, and cardiac insufficiency was seen in six other cases (see Table II).

A well-recognized but rare cause of pruritus is that associated with the reticuloses, particularly Hodgkin's disease. This simple itching in one patient aged 38 was present for a period of 16 months. She had a tiny gland above the clavicle which, when removed at a second attempt, showed the histology of Hodgkin's disease. It has been suggested that there is a sensitization to the malignant glandular tissue. Again, pruritus has been associated with carcinoma of the stomach and prostate. Cardon (1943) records the case of a man aged 89 with a generalized pruritus for three years. The haemoglobin was 43%. A large pyloric carcinoma was found; this was removed, with immediate relief of the itching.

A man of 65 years with generalized itching of three years' duration, not included in Table I, without change in the texture of the skin, was found to have rarified areas in the left scapula strongly suggestive of secondary carcinomatous deposits: biopsy of the scapula revealed an adenocarcinoma. Thus the possibility of a visceral cryptic carcinoma must be considered in a patient of mature age with pruritus, with or without any xerodermatous change in the skin.

The fibres transmitting the sensation of itching pass along the spinothalamic track and have cell stations in the thalamus. The character of itching, with its liability to spread, poor localization, and the production of tension, anger, and restlessness, is distinctive.

In reverse, mental fatigue, tension, and anxiety seem to be able to potentiate the cell station in the thalamus and to lower the threshold of sensation of itching, to encourage its intensity, and to facilitate its spread over the body.

Using histamine to excite itching by intracutaneous injection, Cormia (1952) was able to demonstrate that the threshold value was lowered in normal subjects towards the evening. It was also lowered by psychic trauma, and the itching then became more persistent. Reassurance restored the threshold value to normal.

Emotional Reaction

Thus with every pruritus, if at all sustained, there is an element of emotional reaction, and at the end of the scale are those cases of pruritus in which the emotional, psychoneurotic, or psychotic status is the most important causative factor in the pruritus (see Table III).

TABLE III.—*Incidence of Psychological Factors*

Age	No. of Cases	Psychological Factors and Mental Disorders—i.e., Disorders of Reception and Interpretation
20–39	15	In 5 cases
40–59	13	„ 6 „
60–74	34	„ 12 „

One sign which is a guide to this group is the degree of excoriation that the patient presents. The deep biopsic scratch marks over the face, shoulders, and arms indicate the exaggerated psychological and physical response to the sensation of itching. The investigation of these cases has shown, besides the more common anxiety and tension states, patients with hysterical or obsessive personalities, with paranoia, delusions, or involutional depression. The hysterics use their dramatic ravelled skin to gain their unexpressed desire for comfort and relief from a situation which for them is an intolerable one, physically or emotionally.

One obsessive with severe pruritus was a man who had complained since joining the Army. In civilian life he had always worked hard, all day long. He was unable to do so while in the Army. A similar case was that of a man of 22 who excoriated his face to escape from nasty thoughts and compulsions.

Patients with acarophobia or parasitophobia will present excoriations on the skin, and are convinced that the rolled-up fragments of horn and epidermis which they bring for inspection are living animals which they have felt crawling under the skin and which are responsible for the itching.

A female schoolteacher aged 57, with a two-years history of itching which had begun on the chest and hands and had persisted around the hips, said that she saw flea-like bodies on her skin and thought that they came from the vagina. Other delusions and hallucinations may follow, when the prognosis, especially in the elderly case, is bad, and the patient may need institutional treatment.

If one is dealing with the hysteric and psychotic individual the treatment must be undertaken by a psychiatrist. On the other hand, most cases of psychogenic pruritus occur in those who are amenable to explanation by the practitioner or dermatologist and are capable of insight into the motivation of their disorder. Reassurance and a discussion of business or family worries is often all that is necessary in many cases of anxiety states and tensions. The family practitioner is well able to undertake this task and to offer suitable advice.

Treatment

Treatment with A.C.T.H. or cortisone is not advised for generalized pruritus without inflammatory changes in the skin. Occasionally, in the severe pruritus associated with the reticuloses, these hormones may be indicated and may be the sole means of controlling a most intractable itching.

The antihistamines are widely, perhaps too widely, applied locally to the skin and by mouth. An attempt to be logical in the use of the antihistamines to control generalized itching would include consideration of the aetiology of the pruritus. Thus, if associated with allergy of the mucous membranes to dust, animal hair, or pollen, then diphenhydramine hydrochloride would be valuable. It is recognized that the antihistamines are, in general, powerful sensitizers when applied to the skin and may rarely by mouth give rise to an urticaria or blood disorder—for example, leucopenia. In most cases, apart from serum sickness, the relief of itching is due, one suspects, to the powerful anaesthetic, central depressant, and sedative effects of many of the antihistamines. They are unreliable therapeutic agents in the treatment of pruritus.

The use of sedatives is of value only in those cases of pruritus in which there is an important element of anxiety or tension. Small doses of barbiturate or chloral at night might then be helpful. To attempt to suppress itching by the use of sedatives, particularly in elderly patients, is likely to be a failure. Patients have been seen confused, drowsy, and incoherent, but scratching as vigorously as ever.

The principles of topical therapy are simple. When the skin is dry, hyperkeratotic, or atrophied it should be protected by a greasy application—for example, simple toilet lanolin over limited areas, or a mixture of wool alcohol, hard paraffin, soft paraffin, and liquid paraffin (unguentum alcoholium lanae, *B.P.*). When combined with water up to 50% it is more easily applied and more cooling. Another easily applied base contains emulsifying wax, soft white paraffin, and liquid paraffin (unguentum emulsificans, *B.P.*), to which varying amounts of water can be added to allow of easier spread.

The addition of small amounts of phenol ½%, menthol ¼%, and of tar (liquor picis carbonis, 5 to 10%) may be indicated for short periods to satisfy a demand for active therapy in a patient with a prolonged distressing symptom. Bathing is restricted to avoid maceration and separation of horn, the alkaline irritant effect of soap, and the trauma of towelling. In the elderly, one bath a week is adequate, the emulsifying effect of the bran bag being relied on to cleanse the skin. The skin is partially dried by patting with smooth soft towels and then powdered.

When the texture of the skin is not abnormal the antipruritic agents mentioned above, incorporated in lotions or liniments for their cooling and decongestive effect, may give relief.

The underwear should be loose, of smooth cotton, and the bed warmed at night. Sheets should be smooth and a cradle ensures minimum contact with the body.

The diet should be a non-stimulating one. Tea and coffee are best taken cool and weak, and spices and meat extracts used with care.

Hypnosis

Finally, a word on the treatment of pruritus by suggestion while in the hypnotic state. There is no doubt that the symptom of itching in certain individuals can be kept in check by this method, and both in simple pruritus and in the pruritic dermatoses considerable relief has been obtained.

The best-known exponent of hypnotism (or in the use of animal magnetism, as he called it) was Mesmer, who, Gilbert Frankau (1948) recalls, was born in 1734, twelve years after the last witch was burnt at Leith. A century later Mesmer's activities were described as Satanic when the morality of the subjugation of one man's will to another's was discussed.

The dependence and relationship between the practitioner of hypnotism and his subject is one that can scarcely be described as healthy, particularly in a hysteric. However, there is no doubt that the method can be temporarily effective in pruritus associated with anxiety or tension states.

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The *Medical Journal of the South-West* is the new name of an old friend, the *Bristol Medico-Chirurgical Journal*, which first appeared in 1883. Under the National Health Service Bristol has become the focal point of the South-west Region, and it is considered that the new title will more accurately designate the field from which the *Journal* hopes to glean its sustenance.

AN ACCOUNT OF 2,500 INFANT B.C.G. VACCINATIONS

BY

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The subject of this paper is the personal experience of 2,500 cases of infant vaccination with B.C.G. The material has been drawn from babies born in the Royal Maternity Hospital, Belfast, and the Malone Place Maternity Hospital, Belfast, and has been carried out under the auspices of the Northern Ireland Hospitals Authority and the Department of Child Health, Queen's University of Belfast.

Compared with the recent literature on vaccination against tuberculosis in older age groups, there is little information about infant B.C.G. vaccinations. This is largely due to the fact that vaccination of the infant age group has not been included in the mass vaccination campaigns sponsored by the World Health Organization. In Great Britain, also, vaccination in the younger age groups has hitherto not been extensive.

Selection of Cases

The cases quoted in this study were all vaccinated personally between March, 1952, and March, 1953. Vaccination is offered to every mother for her baby during the lying-in period. The vaccination is optional, but the medical and nursing staffs use their helpful influence, and explanatory literature is freely available. A personal interview is given to any mother who desires it, and to almost every case in which there is a family history of tuberculosis or liability to exposure. Isolation is provided in the hospitals for the babies from birth and throughout the post-vaccinal period when this is indicated.

The live births in the hospitals for the period in question numbered 2,750, and the vaccinations for the same period 2,500, giving an acceptance rate of 92.59%.

Queries Arising During Course of Investigation

As occurs in most investigations, various small problems arose which had not been anticipated and which necessitated some alterations in the original scheme. For example, it became apparent that many of the premature babies had been one, two, and even three months in hospital before being considered fit for discharge. When this fact was realized pre-vaccinal tuberculin skin-testing was instituted if four or more weeks had elapsed between birth and vaccination, instead of omitting all preliminary testing, as is the usual procedure with infant vaccinations.

In addition, having had doubts aroused about the validity of the current belief in the extreme rarity of congenital tuberculosis, a routine tuberculin test is now done on the infants of all tuberculous mothers. It is hoped, at a later date, to publish a report on congenital tuberculosis as a result of an investigation which is now being carried out in these hospitals.

Technique of Dosage and Administration

With regard to technique, dosage, and administration, the recommendations of Winge and Sigrid Holm, of the Central Tuberculosis Clinic, Copenhagen, and of Tolderlund, of the State Serum Institute of Denmark, have been adhered to throughout the survey (Personal communications). There is a tendency in some centres to reduce the recommended dosage in view of the increased liability of infants to develop regional adenitis and abscess formation following B.C.G. injections. This has not been accepted in the present investigations, for two reasons: in the first place the majority of these infants (93.36%) had no known tuberculous contact at the time of vaccination and are unlikely to meet tuberculosis in the first few years of life; secondly, it is admitted (Gaisford, 1953) that the percentage of cases giving a positive tuberculin reaction one year after vaccination falls off enormously if a smaller initial dose of vaccine is given. In this series, in which more than 350 cases have already had the first annual test, there has been no single case in which the post-vaccinal conversion had not been maintained. It is probable, also, that it will not be possible to ensure annual tuberculin testing on a large proportion of these children who hail from all over Northern Ireland, and with the smaller dose the immunity may lapse very soon, while the parents continue to harbour a feeling of false security.

The observation that adenitis is due to an injection which is too deep rather than to too large a dose of vaccine (Palmer and Edwards, 1953) has been confirmed in the present series. Adenitis is almost always due to failure in technique, and the reason that it is more frequent in the infant age group is that it is technically more difficult to get a true intradermal injection in these subjects.

The infants in this series therefore received 0.1 ml. of vaccine—that is, 0.075 mg. of B.C.G.—intradermally in each deltoid region.

With the exception of premature babies, or some ill babies, or those with birth injuries or congenital abnormalities, all were vaccinated between the first and the eighth day from birth. It is desirable that the infant be removed from its cot for the purpose and that the top part of the trunk and arms should be bared. Before these precautions were taken a few babies were vaccinated too high in the arm, and the adenitis, when it occurred, affected the cervical glands rather than the axillary ones, which is unfortunate for cosmetic reasons and also because these glands are more likely to suppurate through being subjected to frequent nasopharyngeal infective onslaughts.

Post-vaccinal Examination

Post-vaccinal testing is carried out at the Royal Belfast Hospital for Sick Children eight weeks after vaccination, at a special clinic reserved for these babies. The attendance rate at this clinic is about 85% of the original number vaccinated. I am indebted to physicians of the chest clinics throughout Northern Ireland, and most particularly to the health visitors of the Northern Ireland Tuberculosis Authority, for carrying out the tuberculin skin tests on babies whose parents live a great distance from Belfast, and also on the defaulters nearer home.

On the occasion of the visit to the hospital for post-vaccinal testing, mothers are invited to bring older children for preliminary testing if they so desire. The facility is made use of to a considerable extent, and it is interesting to record that a definite, albeit small, proportion of siblings of 3 years and under are Mantoux-positive at this examination. By this means some cases with a definite primary tuberculous complex have been revealed, though in the majority there was no known source of exposure, and the parents and other household inmates were radiologically free from tuberculosis. Two of these cases were from farms, and the children in question had been reared on unboiled milk from untested cows; the infection may therefore well have been bovine in origin.

At the post-vaccinal examination routine questions are asked about neonatal health. In no case has there been reason to suspect any constitutional disturbance as a result of the vaccination, although whooping-cough, broncho-pneumonia, gastro-enteritis, operations for congenital pyloric stenosis, and transfusions for erythroblastosis have all been experienced during this period. In spite of advice to the contrary, many of the babies have already had their smallpox vaccination when they return to the clinic, and apparently without adverse effect.

The vaccination sites are examined and a search is made for evidence of regional adenitis. The conversion rate at

the time of post-vaccinal testing is 99.69%. Only seven cases gave a negative result to the tuberculin skin test. In one of these there was no local evidence of vaccination, and it is probable that the child was not vaccinated, but that a card was filled in and filed in error. In the case of the remaining six, four were reported on by local practitioners and two by health visitors; it has not been possible to see the babies in question personally or to repeat the test or confirm the negative findings with a Mantoux 1/100. Table I gives an analysis of the results in this series.

TABLE I.—*Analysis of Findings*

Vaccinations			2,500
Complete:			
With post-vaccinal control		2,331 (93·24%)	
Successful, with positive P.V. test		2,324 (99·69%)	
Unsuccessful, with negative P.V. test		7 (0·31%)	
Incomplete:			
Without post-vaccinal control		169 (6·76%)	
Untraced	145		
Dead	24		

Premature Babies, or Babies with Congenital Illnesses or Abnormalities

Approximately 12% of the vaccinated babies are premature and inhabit the nursery wing of the Royal Maternity Hospital. A birth weight of under 5½ lb. (2.5 kg.) is accepted as the criterion of prematurity. As already stated, some of these babies have been a considerable time in hospital before vaccination. Discharge takes place when they are 5½ lb. if otherwise thriving and the home conditions are reasonably good. Consequently, the premature babies are vaccinated when they are in or about this weight. There has been no difference in the post-vaccinal behaviour of these infants as compared with full-term ones, and no greater incidence of adenitis.

Babies with congenital abnormalities or diseases—for example, spina bifida, hydrocephalus, mongols, cretins, infants with retrolental fibroplasia, or haemolytic disease—are all included in the vaccination programme, provided that the physician in charge considers that they are likely to survive the first few months of life. This perhaps is a mistake from the statistical point of view, as it follows that the overall death rate of these infants will be higher than the average infantile mortality rate; but this is offset by the fact that it impresses on the parent the idea of the vaccination being a normal routine procedure. It also ensures that the handicapped child, if it survives, will not be at any disadvantage compared with its more fortunate brother when and if exposed to tuberculosis.

Table II gives the number and percentage of deaths in our series of cases and the cause when this could be ascertained.

TABLE II.—*Deaths*

Belfast City death rate (1952) under 1 year=44 per 1,000 live births		
Deaths in present series of 2,500		24 (0·96%)
Infanticide	1	
Haemolytic disease	2	
Virus infection	1	
Gastro-enteritis	3	
Bronchopneumonia	2	
Congenital abnormalities	2	
Premature, within two weeks of discharge	2	
Unknown cause; neighbour's report	11	

Tuberculous Contacts

There was either a tuberculous contact in the household or a family history of tuberculosis in 166 (6.64%) out of 2,500 vaccinations. Table III gives a summary of these. Where required isolation was carried out (*a*) by keeping the infant in hospital till tuberculin conversion occurred; (*b*) by keeping the infected relative in hospital or away from the home; or (*c*) by arranging for the baby to be kept, for the post-vaccinal period, in an uninfected household or child hostel. Many of the mothers concerned came from the sanatorium for their confinement, returning there afterwards. They do not handle the baby at any time.

Four infants had contact with active though hitherto unsuspected sources of infection during the post-vaccinal period. These have been the subject of two-monthly review, but no signs of tuberculosis have yet been discovered in any of them, and chest *x*-ray films have all been normal.

TABLE III.—*Contact of Family History*

No. of contacts		166 (6·64%)
Relationship of contact:		
Parent	97 (58·5%)	
Grandparent	17 (10·2%)	
Aunt or uncle	29 (17·4%)	
Sibling	12 (7·2%)	
Other	11 (6·7%)	
Isolation required in 64 (2·56%)		

Regional Adenitis and Abscess Formation

Regional adenitis or abscess occurred in 46 cases (1.84%) of this series of 2,500 infants. This is a minimal estimate, as no doubt there have been other cases which have been treated elsewhere and are not personally known at the clinic. Table IV summarizes the incidence, treatment, and also the bacteriological report where available.

TABLE IV.—*Incidence of Regional Adenitis Among 2,500 B.C.G. Vaccinations in Infants*

Cases of regional adenitis			46 (1·84%)
Single	27		
Multiple	19		
Simple adenitis		28 (1·12%)	
Adenitis with abscess formation		18 (0·72%)	
Spontaneous rupture	3		
Incision required*	15		

*Bacteriology of pus: B.C.G. recovered, 4; other organisms, 4; sterile, 4; no information, 3.

As previously mentioned, it is considered that in most cases this complication occurs as a result of faulty technique, where a greater or less amount of vaccine is injected subcutaneously instead of intradermally, and this is especially apt to occur in babies well endowed with subcutaneous fat.

In qualification of this statement with regard to technical failure, it should be noted that the strength and viability of the organism in the vaccine culture are not as constant as assurances would lead one to believe. In this series covering 13 months, in which 56 weekly batches of vaccine have been used, adenitis occurred in 14 different or consecutive batches of vaccine, whereas without this factor being involved one would expect a more even distribution of the complication.

Experience shows that if abscess formation occurs in the first eight weeks after vaccination it is usually due to secondary infection of the vaccination site; if it occurs within six months B.C.G. organisms are almost invariably recovered from the pus; whereas if it occurs after this period the pus is usually sterile.

Treatment of the adenitis is conservative. If an abscess is red, tense, and points on the skin it is dealt with by simple incision and evacuation, and the application of a sterile dressing. Formerly these abscesses were aspirated as recommended by the Danish authorities, but this practice has been abandoned in favour of incision and would appear now to be more generally acceptable. No abscess has had to be reopened, though a second abscess in the same child at a different site has occasionally required incision. Even in cases with multiple abscesses there has not been any case in which the infant's general health has suffered or in which the hilar glands have been involved. A few cases have been reported at the clinic after spontaneous rupture; these have been treated with ultra-violet light and have dried almost immediately, and healed after half a dozen exposures. In a small proportion of cases in which superficial ulceration at the site of the local lesion has discharged for more than a week it has almost invariably been found that an occlusive elastic dressing has been applied at home. This tends to produce a weeping eczematous area around the vaccination, and should be replaced by a loose piece of sterile gauze or lint. The discharge then ceases and the lesion heals.

Summary and Conclusions

This study presents the findings in 2,500 consecutive cases of infant vaccination against tuberculosis with B.C.G. vaccine. The normal procedure with uncompli-

cated cases is discussed, and also the different procedures involved in contact cases and with premature infants.

The complications of vaccination have been estimated and the methods used for combating them are described. A personal view is submitted regarding the desirability of adhering to the recommended dosage. The infant mortality in this series is compared with the death rate in infants under 1 year for Belfast city.

In conclusion it is shown that since the introduction of infant vaccination with B.C.G. no anxiety has arisen and no major problems have had to be overcome. In addition, it is an admirable and simple way of further propagating information about the prevention of tuberculosis in a population which is already very conscious of the problem. There has been an excellent and increasing response to the introduction of B.C.G. among parents, and it has, in general, been warmly welcomed by practitioners and health authorities alike. It will be for posterity to judge the ultimate value of this preventive measure. A most careful follow-up of these cases is indicated.

I have to thank all my colleagues, obstetrical and paediatric, for their co-operation in this work, and particularly Professor F. M. B. Allen for his unfailing support and encouragement in the use of B.C.G. vaccine in Northern Ireland.

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CHANGES IN SKIN RESPONSE IN ASTHMA

A SKIN-TEST FOLLOW-UP OF ASTHMATICS

BY

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The use of skin-testing as a method of diagnosis in asthmatic patients, while generally accepted and more or less implicitly relied on by specialists in allergic disease, is still a controversial topic among general physicians and general practitioners. The idea of determining the sensitivity of the bronchial mucosa by applying the suspected agent in one way or another to the epidermis is to many somewhat fantastic. It is, of course, now generally recognized that allergic sensitivity is only one of the aetiological factors in the asthmatic reaction, but it seems to be equally widely agreed that it is an important one.

The disagreement comes when an attempt is made to assess just how important it is. The unbiased observer who nevertheless has some experience of the investigation and treatment of asthmatic persons would probably sum up the position by saying that it all depends. In some patients allergic sensitivity is the major cause of the symptoms; in some it is one among several equally important factors; and in others it is of no importance at all. In the present article this view is accepted as probably correct.

The survey and analysis presented are an attempt to contribute towards the answers to two questions: (1) What changes, if any, occur in skin reactions over the years? (2) What is the significance, if any, of such changes (or, alternatively, the absence of any changes) in relation to the clinical progress of a series of asthmatic patients?

From a personal study of the literature, as well as from a careful search kindly made for me by the Library of the Royal Society of Medicine, it seemed that such a combined follow-up of a series of cases had not, so far, been carried out.

For some years I have conducted a special out-patient session, to which I can refer those persons suffering from bronchial asthma who attend my general out-patient morning session. This originated from experience of the chaos caused in a general out-patient clinic by an attempt to investigate and advise the asthmatic patient on the spot. Inevitably clinical material accumulates in such circumstances, and one is faced with the obligation to analyse it.

Skin-test Method

An early problem confronting anyone who attempts to do more than pacify the asthmatic and his relatives is the skin-test method. How important is it? What does it mean? At first I took the view that it probably had a place in the confirmation of allergic sensitivities suggested by the history of the case. I was warned that most people would show reactions, and that I would either be deceived or merely confused by the high proportion of positive results. It was therefore with some surprise that I found my difficulty to be the large number of negative results in patients with strongly "positive" histories. The potency of the solutions used seemed to be proved by the intensity of the reactions when they did occur.

Confidence in the method as a valuable aid to diagnosis naturally declined, and for a number of years relatively few patients were investigated in this way. However, clinical experience forced one to the conclusion that allergic sensitivity was a most variable quality, appearing, disappearing, and varying in an inconsequential manner, for which the skin-testing method could not be blamed; and it seemed worth while to see if this was clearly shown in the records of those cases which were available. About six years ago, therefore, a number of energetic skin testers, armed with a battery of syringes, were assembled, and those patients previously tested were summoned. The response was so poor that the survey did not yield any significant results.

It was therefore determined to carry out a minimum routine number of skin tests on every adult patient attending, and to repeat the follow-up testing on a larger series at a later date. This has just been done, and the results, though not as numerically valuable as was originally hoped, are interesting enough to warrant publication.

The actual testing was carried out by two independent observers, who also noted the patient's own assessment of his symptoms over the intervening years since the previous testing. I did not see the patients at all when they attended for this special purpose, and the observers who did see and test them took no part whatever in the original assessment, the original testing, or in the analysis.

The tests carried out in this series were group mixtures for the most part, including the common inhalant allergens (household dusts, clothing materials, pollen dusts, etc.), but excluding foodstuffs. Friedewald (1952), in a study of 1,900 cases, came to the convincing conclusion that skin-testing with solutions or other preparations of foods was so much waste of time. No apology is therefore made for the policy adopted in this connexion, nor is it thought necessary to go into all the arguments for and against the testing of foods by any method other than that of dieting.

The survey comprises only a small proportion of the total number of cases attending the special out-patient session, and indeed not many of those in whom skin tests had been

at one time made. Many patients did not attend the skin-testing sessions, which were arranged for the purpose of this investigation, saying that they were now well, did not require any further attention, and were afraid that any injections might cause a recurrence. A few complained that they were no better, and did not believe that they would receive any benefit from a repetition of the tests. The attendance of the "unimproved" group was generally good, however. There is thus some bias in favour of the unimproved cases as a whole; but this bias is not important for the present purpose.

Results

It is possible to survey the results in 209 cases, followed up over varying periods up to 17 years, the shortest period being two years, and the average seven years. This period is long enough to allow any variations in skin sensitivity to manifest themselves, and the number, though not large, has been found adequate for the immediate purpose.

Some general figures may be given before the general analysis is described. Of the 209 subjects available for analysis, 31 were under the age of 15, mostly between 12 and 14 (Table I).

TABLE I

Condition	No.	No. Under 15
Improved	138	25
Unchanged, or slightly improved	55	6
Worse	16	0
Total	209	31

It should perhaps be stated that improved means a very considerable change for the better—one quite outside the normal shift of symptomatic emphasis so often shown by the asthmatic person. For example, a patient must have been free of attacks for over a year, or have reached a state in which attacks of moderate or slight severity occur only occasionally. Lesser degrees of improvement are placed among the unimproved group, the changes being regarded as within the limits of normal variation.

Of the 209 cases, 21 had received "desensitizing" injections, 5 being under the age of 15. These 21 patients all showed a change in skin reactions from positive to negative shortly after the injections. It is of interest to note that the reactions had reverted to the original state in eight.

Thirteen of these cases were improved and eight unchanged or only slightly improved. These eight patients included five in whom the skin reactions had reverted to the original state.

In five cases a "combined" reaction was observed. By this is meant changes in both directions. Four of these were improved, and the remaining patient was unchanged. These five patients have been excluded from the analysis, leaving 204 cases to be classified. In 21 patients the result was difficult to place. In these, a change in one direction or the other occurred in some of the tests, but not in all. For example, a patient in whom the test was completely negative on the first occasion would yield a strong positive reaction to one or more pollen solutions at the final follow-up test, the other tests still showing negative results. In such a case the change in the pollen reaction was regarded as significant, and the case was placed in group 3 (−to+).

Another problem was presented by patients who yielded several positive reactions at the first test and who at the final test showed negative results to all except one of the formerly positive solutions. This type of change was somewhat of a puzzle as regards classification, and each case was judged separately on its merits. If the remaining positive reaction was a really strong one, then the patient was placed in the "unchanged" group, but if it was less convincing he would be placed in group 2 (+to−).

All tests were carried out by the intradermal method, using a dose of 0.1 ml. A positive reaction means a definite weal of at least the size of a silver threepenny-piece, with pseudopial irregularities and surrounding erythema. Any "weal" of smaller size, or one without pseudopodia or erythema, was disregarded.

TABLE II

	Results of Skin Tests	No. Tested	Clinical Progress		
			Improved	No Change	Worse
Group 1	No change	114	74 (65%)	31 (27·2%)	9 (7·0%)
„ 2	+ to −	40	26 (65%)	13 (32·5%)	1 (2·5%)
„ 3	− to +	50	34 (68%)	10 (20%)	6 (12%)
	Totals	204	134	54	16

Table II shows the similar composition of the three groups when analysed according to clinical progress. There are, it is true, minor variations. For example, the percentage of patients whose condition had deteriorated over the period of study is highest in group 3 (12%) and lowest in group 2 (2.5%). The small total number of these worsening cases (16 in 204) makes any conclusion based on percentages of very doubtful validity, however. It will be noted that in this group, although the difference is slight, the improved cases also are relatively numerous.

The improved cases are of almost exactly the same percentage in each group, and those showing no significant change in either direction do not differ significantly from one group to another, although in group 3 there is the natural reflection of the higher numbers of improved and worse cases, in the lower relative proportion of the unchanged.

Discussion

It seems permissible to draw certain conclusions from the evidence that is here presented. In the first place, it is clear that the skin-test response is a variable quality, former skin sensitivity disappearing and new sensitivities arising as time goes on. This is in general accord with clinical experience in allergic conditions, although the correspondence between the clinical variations and the skin reactions is often far from close. The most common example of this divergence is the persistence of seasonable asthma long after the skin reactions to all pollens become negative. It is nevertheless evident that skin sensitivity is not a static quality.

Secondly, it is apparent that negative skin reactions may alter to positive in association with no corresponding clinical change, with well-marked improvement, or with deterioration; and that the chances of each of these variations occurring is about the same as it would have been had the skin reactions altered in the opposite direction or not at all. Skin-testing on the whole, therefore, seems to be an unreliable indication of clinical progress, and of little or no prognostic value.

The two questions posed at the beginning have therefore been answered by the survey and analysis which has been made.

It seems natural, and possibly useful, however, to consider briefly the relationship between allergic sensitivity in asthma and the skin-test response. It is recognized, as has already been stated, that allergic sensitivity is but one of the factors which influence the clinical progress of the asthmatic. The exact role of allergic sensitivity in this or, indeed, in any similar series cannot be stated with real accuracy, unless it may be assumed that the skin-test response is of pathognomonic significance in every case. Without such a "yardstick" the classification becomes too much a matter of personal opinion for reliable statistical analysis.

If skin sensitivity is accepted as the criterion it would seem that allergy was a dominant or important feature in a small minority of the cases in the present series; otherwise the

results would have been expected to show at least some significant correlation with the clinical condition of the patients.

It is true that this study does not provide enough evidence to enable one to judge the reliability of the skin-test response as an indication of allergic sensitivity in asthma; and the literature, vast as it is, does not give us a clear and unequivocal answer. It would, however, seem fair at least to say that the absence of any significant relationship of change in skin sensitivity to clinical progress in this series of asthmatic patients may not necessarily indicate that allergic sensitivity was an unimportant factor in the series as a whole, and that the skin response is perhaps not a completely reliable indication of allergic sensitivity. On the other hand, it must be said that in a number of cases skin-testing may give valuable and helpful information—always provided that its significance is judged in relation to all other available information.

Summary

The skin-test responses to the common inhalant allergens were followed in 209 asthmatic patients (of whom 31 were under the age of 15) over an average period of seven years, with extremes of 17 and 2 years, and were compared with the clinical progress of the patients.

The series was, as a whole, somewhat biased against the "improved" cases by the reluctance of asthmatic persons who were well to submit themselves to "repeat" skin-testing. This was not found, however, to affect the purposes of the survey and analysis.

Of the 209 cases, 138 were improved (no asthma for at least one year, or only occasional or moderate attacks at infrequent intervals), 55 were unchanged (or slightly improved), and 16 were worse.

The skin-test responses were found to have altered widely or significantly in 90 of the 209 cases.

These changes in skin sensitivity were found, however, to bear little or no relation to the clinical progress of the patients.

Skin-testing may not be a completely reliable indication of allergic sensitivity in general, but in the individual case it may give valuable information if used with discretion.

I am grateful to Dr. Christopher Strang and Dr. Michael Evans, who carried out the follow-up skin tests; to the Librarian of the Royal Society of Medicine and his staff, who kindly conducted a detailed research of the literature; and to Mr. Campbell, of the Department of Industrial Health in the University of Durham, who kindly checked the statistical analysis.

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The new neurosurgical theatres and extensions to the department of neurosurgery, which Sir Geoffrey Jefferson, F.R.S., opened at Frenchay Hospital, Bristol, last October, are now in commission. The theatres embody many modern improvements. Full air-conditioning on a plenum system has been installed, which provides 16 changes of air per hour, the intake being high above the roof and the air filtered. Glass-screened galleries help reduce aerial contamination by spectators, and allow a 70° angle of view on to the operation field. Communication with the galleries is by throat-microphone. The twin operating theatres share a common instrument store and sterilizing rooms; in the latter there are special arrangements to prevent excessive humidity. The department, which is the base for the neurosurgical service of the South-western Hospital Region, will ultimately have accommodation for 72 patients, including children.

INVESTIGATION OF AN OUTBREAK OF BOVINE TUBERCULOSIS IN A RURAL AREA IN LEICESTERSHIRE

BY

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The *British Medical Journal* (1953) again drew attention to the importance of tuberculosis of bovine origin when it summarized in a leading article a survey undertaken by the Medical Research Council on this problem (Wilson *et al.*, 1952). The survey showed that tuberculosis of bovine origin still remains a serious problem. It was estimated that in 1944 there occurred 550 deaths in Great Britain from tuberculous meningitis and 1,050 deaths from other varieties of non-pulmonary tuberculosis due to infection by the bovine type of bacillus. It is realized that a survey at the present moment would not show such a high mortality, on account of the effects of streptomycin and P.A.S., but it is logical to assume that the amount of illness and disability from infection by the bovine bacillus still remains a very great problem. The survey showed that such infection occurred more often in children between the ages of 5 and 9 years. It was suggested that this could be explained by the fact that, whereas infants had previously been fed on cows' milk when breast-feeding failed, now, largely through the efforts of welfare clinics, they are fed on dried or other safe forms of milk, and it is when the child goes to school and moves around in other households that the possibility of infection from raw milk may arise. That leading article has stimulated us to report a recent survey which was undertaken in a rural Leicestershire area where there seemed to have been an abnormal incidence of tuberculosis associated with a known source of infection from a single cow in an otherwise healthy herd.

In January, 1952, notifications were received of two cases of non-pulmonary tuberculosis in children aged 9 and 5 living in the same village (Cases 1 and 2). Abdominal glands were evident in one and cervical glands in the other. The occurrence of these two cases in the same village at the same time led us to inquire from the chief county sanitary officer about the milk supply for these two households. It was found that both children were obtaining milk from the same source, and it was reported that on December 20, 1951, a routine biological sample of milk from this source contained tubercle bacilli. On December 22 a clinical examination of the herd was carried out by the divisional veterinary officer, and this revealed that a cow in the herd was suffering from tuberculosis of the udder. This cow was slaughtered under the Tuberculosis Order of 1938.

Since most of the children in this area were obtaining their milk from this known infected source, inquiries were made to find other children who might be suffering from tuberculous glands of the neck and other tuberculous conditions, and at the same time it was thought

advisable for a tuberculin survey to be undertaken of all children in the area. In addition to the two original cases of tuberculosis a further three children were found to have tuberculous glands of the neck which required treatment.

Case Reports

Case 1.—A case of tuberculous glands of the abdomen in a boy aged 9 was notified on January 18, 1952. Six weeks before examination he had erythema nodosum and later abdominal pain. He was seen by Dr. J. V. C. Braithwaite, who diagnosed tuberculous abdominal glands.

Case 2.—A girl aged 5 developed a gland on the right side of her neck in October, 1951, and was later admitted to the Leicester General Hospital, where the gland was excised and found to be tuberculous. The child was subsequently treated with streptomycin and P.A.S., making an uneventful recovery. This case was notified on January 21, 1952.

Case 3.—As a result of our inquiries a boy aged 14 with an enlarged gland in the neck was referred to the Leicester County Chest Clinic by his general practitioner on February 6, 1952. His history was that in September, 1951, he developed a gland at the right side of his neck which at first settled down. When he was first seen at the clinic the Mantoux test was strongly positive, but the gland itself did not seem to require any active treatment, although his tonsils were somewhat enlarged. These were removed and found to be tuberculous. In January, 1953, the gland increased in size, and after a preliminary course of streptomycin and P.A.S. it was excised.

Case 4.—A girl aged 4 was referred to the Chest Clinic on April 2, 1952, with a history of repeated sore throat for the past five months. She had a gland at the left side of her neck and an enlarged tonsil on that side. The tonsils were removed and culture revealed tubercle bacilli of the bovine type. The gland has since settled down without any further treatment.

Case 5.—A child aged 2 who was tuberculin-positive when we undertook the survey developed a gland in the right side of the neck two months later. This increased in size and was treated with streptomycin and P.A.S., and finally by excision. This case is interesting because it is the only one of the five which presented no clinical signs at the time of the survey but subsequently developed clinical evidence of tuberculous adenitis.

Commentary

At the time of writing we have these five clinical cases of tuberculosis arising in children, all of whom had been obtaining milk from the same source and whose infection can, in our opinion, be directly attributable to a tuberculous cow.

We decided that the problem should be investigated as soon as the first two cases were notified from the same village. The population of the area is 9,660 people, scattered in 31 villages over an area of 45,000 acres. Two of these villages have a population of about 1,600; two have between 600 and 900; 12 have 100 to 500; and 15 have fewer than 100. In the area there were 154 milk producers, of whom 38 retailed their products. For two years prior to this outbreak all raw milk sold in this district had been sampled quarterly and subjected to examination for living tubercle bacilli by guinea-pig inoculation. By this means four infected milks had been discovered and the appropriate action taken. In the particular herd with which we are concerned one of us (R. W. K.) found that the customary veterinary inspection due in July, 1951, had not been carried out and that the infected cow had been under treatment for at least four weeks before its detection in December, 1951. It therefore seemed likely that the milk from this herd, which was bulked together, had contained tubercle bacilli for several weeks before bacteriological confirmation was available, and that the consumers in this area had been exposed to the risk of infection for a period of several months. The producer made available to us his register of customers, which showed that he supplied 106 families in five villages, including 63 children under school-leaving age.

The five villages catered for by this particular supplier, together with seven other villages, send their children between the ages of 5 and 11 years to one central primary school, and from there, at the age of 11 plus, they pass to an adjacent secondary modern school, where they are joined by children of a similar age from a further 32 outlying villages. It was administratively easy to investigate the entire child population of these 12 villages, but the whole of the older children's school was included in the survey, in order to distract attention from the local nature of the real investigation. Since the majority of the older children attending the secondary modern school lived in villages too far away from the area at risk for their tuberculin results to be of any statistical significance in this survey, they are not included in any of the tables in this paper.

The county medical officer circularized all parents in the area, pointing out the desirability of such a survey, and at the same time he advised the general practitioners that such a survey was to be undertaken and asked for their co-operation. The co-operation of the parents and general practitioners was readily given and was universal in the villages at risk. The refusals received were from parents of older children coming from outside the infected area. It is interesting to see how much co-operation can be obtained in a survey of this nature; the response is shown in Table I.

TABLE I.—*Parent Co-operation*

Age Group	Total No.	Refusals	Absentees from Testing	No. Tested
Under 5 years ..	123	—	5	118
5–7 ,, ..	61	—	—	61
8–11 ,, ..	63	—	—	63
12–15+ ,, ..	37	—	—	37
Total ..	284	—	5	279

The high response in the age group under 5 was largely due to the fact that the health visitor personally visited many of the houses to carry out the tuberculin test. The method of tuberculin testing was that in children under the age of 10 Allen and Hanburys' tuberculin jelly was used in the routine manner—that is, the skin was cleaned with acetone and rubbed gently with flourpaper. In children over the age of 10 we contented ourselves with a single dose of 1/1,000 of old tuberculin. The results of the survey are shown in Table II. All children who were tuberculin-positive were *x*-rayed by the mass radiography unit; no abnormalities were found. The outstanding points in Table II are the variations between groups A and C, which clearly demonstrate the beneficial effects of a milk supply which is known to be safe (group C). Group A indicates what may occur when there is a known infected supply. We do not intend to introduce any discussion on the alleged

TABLE II.—*A Summary of Test Results*

Village Group	Under 5 Years			5–7 Years			8–11 Years			12–15+ Years		
	Pos.	Neg.	% Pos.	Pos.	Neg.	% Pos.	Pos.	Neg.	% Pos.	Pos.	Neg.	% Pos.
A (infected)	18	10	64·2	10	6	62·5	11	0	100	8	0	100
A (other) ..	3	11	21·4	1	7	12·5	9	11	45·0	9	6	60·0
A Total ..	21	21	50·0	11	13	45·8	20	11	64·5	17	6	73·9
B	14	23	37·8	7	12	36·8	3	9	25·0	5	3	62·5
C	3	36	7·6	4	14	22·2	1	19	5·0	3	3	50·0

Group A = Five villages at risk—subdivided into group A (infected), those children known to have been supplied from the infected source; and group A (other), the remaining children in these villages not receiving milk from the infected source.
Group B = Five adjacent villages; no known source of infection.
Group C = Two adjacent villages; milk supply known to be safe.

value of drinking raw milk as a means of immunization, but merely mention it in order that we may dismiss it as a tragic form of immunization.

The Medical Research Council (1952) published the results of a national tuberculin survey which was undertaken in 1949–50, and, while no figures are given for those under 5, the figures for a rural area in the age groups indicated showed a tuberculin sensitivity rate as follows: 5–7 years, 26.5%; 8–11 years, 35.6%; 12–15 years, 50%. Compare these with our figures, which were also taken from a rural area but which are not unnaturally boosted up by this known source of infection. Hall (1950) did a similar survey on children in a village where there was a proved source of infection associated with a tuberculous gland; his results are shown in Table III. In this particular outbreak the

TABLE III.—*Results in Hall's Survey*

	Children Tested	Positive	Negative
Age 0–1	60	41 (68·3%)	19
1–4	7	1	6
5–15	15	12 (80%)	3
	38	28 (74%)	10
All 1–15	53	40 (75%)	13

milk supplier had served the school as well as the village. In the Leicestershire survey the milk supply to the school was from an outside approved source.

As most of us in the tuberculosis service feel we are approaching the possible end of tuberculosis as a major problem in the community, it does seem more evident than ever that there is absolutely no justification for bovine tuberculosis playing such an important part in the incidence of tuberculosis. Not only may the bovine type cause a mortality of well over 1,000 a year in Great Britain, but it produces many crippling forms of tuberculosis. John Francis (1947) states that, according to the most reliable estimate, 20% of cattle in England are tuberculous, 7.5% in Wales, and 14% in Scotland. The incidence in dairy cows is probably 30 to 35%, but there is a great deal of variation in incidence in various parts of the country. It is lower in Wales, the North and South-west of England, and the North of Scotland. The Midlands of England are the most heavily infected. Furthermore, he states that complete healing of lung lesions is much less common in cattle than in man. He estimates that probably 0.5% of all cows in Great Britain have tuberculosis of the udder, and it is this type of tuberculosis which is the most important from the point of view of milk-borne infection. The result of infection in a small community by a single cow such as we have described emphasizes the need either for ensuring that the milk supply throughout the country must eventually come from accredited tuberculin-tested herds or for the general pasteurization of milk.

Conclusion

This survey demonstrates the following facts as well as the statistical data outlined.

(*a*) The importance of close liaison between the chest services and the local authorities in the prevention of tuberculosis. The chest physician can deal with a problem such as this only by obtaining the fullest assistance from the county medical officer and the staff of the county health department and the district medical officer of health.

(*b*) The desirability of a tuberculin test in all cases of glands of the neck. In our opinion this should become a routine: it is a very simple procedure, and any chest clinic would willingly undertake the necessary investigation. It must be borne in mind that only about 50% of cases of tuberculous adenitis are, in fact, bovine in origin. The tonsil is the recipient of the human bacillus by inhalation and the tonsillar glands are subsequently involved. This fact was proved by the classical work of A. S. Griffith (1937, 1938).

(*c*) The high response of such a survey can be obtained only if the parents, general practitioners, and school authorities are all acquainted with the problem, and it is hoped that this article will show the willingness of both the local authority and the chest service to investigate any such similar outbreak and will again prove that the notification of a case of tuberculosis may have much wider ramifications than at first supposed.

We wish to acknowledge the help given to us by Dr. G. H. Gibson, County Medical Officer of Health for Leicestershire, Mr. S. A. Gregory, Chief County Sanitary Inspector, and all the other members of the County Health and Education Department who assisted us in making this survey as complete as possible. We also thank Dr. J. V. C. Braithwaite, Mr. T. M. J. d'Offay, and Mr. N. E. Kendall.

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DIAGNOSTIC DIFFICULTIES IN CONSERVATIVE TREATMENT OF PERFORATED ULCERS

BY

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It was only 60 years ago that Hastings Gilford treated a case of perforated peptic ulcer by operative closure—the first case so treated in this country. Since then this has become the accepted method and, until recently, the only method; but for some time a conservative regime has been advocated by a few authorities (notably Hermon Taylor, 1946, 1951).

The prerequisite of any form of treatment is accurate diagnosis, a problem which, in this matter, troubles us to-day almost as much as it did Mikulicz at the end of the last century. He indeed, before performing laparotomy, confirmed his diagnosis by puncturing the distended abdomen with a trocar.

Gastro-duodenal perforation causes the clinical syndrome of acute peritoneal irritation, hence the problem of accurate diagnosis consists first in eliminating the various extra- and intra-abdominal conditions which may simulate peritoneal irritation—for example, tabetic crisis, diaphragmatic pleurisy, coronary infarction, acute cholecystitis—and, second, in eliminating the other conditions which also cause peritoneal irritation.

If the treatment be conservative a misdiagnosis of one of the first group of conditions is not likely to be a tragic error, but a misdiagnosis of one of the second group may well be. On the other hand, if the treatment is to be operative a misdiagnosis of one of the first group will lead to an unnecessary and possibly dangerous procedure, whereas a misdiagnosis of one of the second group will automatically be corrected at operation.

Present Investigation

It is with the second group of conditions that this paper is concerned. Seventy consecutive cases of "widespread peritoneal irritation" are presented: "widespread" because the term "generalized" is regarded by many as synonymous with impending death, and "irritation" because that is a clinical term, and "peritonitis" is an inflammatory reaction generally, though not accurately, believed to be associated with infection.

The 70 cases fall into the following groups:

1.	Gastro-duodenal perforations		34
	Duodenal ulcer	22	
	Gastric ulcer	7	
	Stomal ulcer	1	
	Carcinoma	4	
2.	Appendicitis		17
	Without abscess	13	
	Intraperitoneal rupture of abscess	4	
3.	Haemoperitoneum		9
	Tubal pregnancy	4	
	Ruptured liver	2	
	Ruptured spleen	1	
	Ruptured left gastric artery	1	
	Ruptured ovarian cyst	1	
4.	Perforated small bowel		2
	Jejunal diverticulum	1	
	Multiple chromaffinomata	1	
5.	Perforated large bowel		6
	Spontaneous perforation of pelvic colon	1	
	Carcinoma of caecum	1	
	Carcinoma of descending colon	2	
	Diverticulitis of pelvic colon	1	
	Radionecrosis of pelvic colon	1	
6.	Lesions of female genital tract		2
	Salpingitis	1	
	Intraperitoneal rupture of tubo-ovarian abscess	1	

The purpose of this investigation is as follows. (1) An attempt is made to derive from a study of the clinical features of the gastro-duodenal perforations a "diagnostic screen," to be applied to all cases diagnosed as "acute peritoneal irritation." (2) The diagnostic screen is applied to those cases of "acute peritoneal irritation not of gastro-duodenal origin" which were pre-operatively considered as probably or possibly suffering from gastro-duodenal perforation. The persistent diagnostic error is noted. (3) The results of treatment of all cases by laparatomy are considered, to find out how many of those with gastro-duodenal perforations succumbed because of the operation, and how many of the other patients with peritoneal irritation survived when laparotomy was not delayed by a mistaken initial diagnosis. (4) In the light of these findings, the advisability or otherwise of the non-operative method of treating gastro-duodenal perforations is considered.

Main Features

The principal features of the cases of perforation were as follows:

Of the 34 cases, 27 were male. The average age was 49 years, with extremes of 17 and 73 years. The temperature averaged 98.1° F. (36.7° C.), ranging from 97° F. (36.1° C.) to 100.2° F. (37.9° C.); the pulse averaged 80 (48 to 120); and the respirations averaged 22 (18 to 40).

Previous Dyspepsia.—Twenty-nine cases had a previous history of dyspepsia. One case had had a previous perforation closed and a gastro-enterostomy performed. Four cases had had previous perforations with simple closure only.

Exacerbation of Symptoms immediately before Perforation occurred in 28 of the cases; there was increased dyspepsia for one to several days before the actual perforation occurred.

Sudden Onset.—All patients were able to state the exact time of onset—for example, "I had just laid down the newspaper, when suddenly . . ."

Time of Onset.—All but five cases occurred during waking hours.

Duration of Acute History.—The average time was five and a half hours, with extremes of one and fourteen hours; these times do not show the delay in "calling the doctor," but the delay from onset to examination in hospital.

Trauma.—In only one case was trauma present. This patient walked into the casualty department and stated that he "strained the abdominal muscle lifting a heavy weight and it has given way."

Easing of Pain.—In only seven cases had the pain eased off.

Site of the Pain.—In 18 cases the pain was indicated as epigastric, in 15 cases generalized, and in one case in the right hypochondrium.

Vomiting.—Eighteen of the patients had vomited, some excessively; 16 had not.

Bowels.—There were no cases of diarrhoea. Six cases had constipation, and 28 had normal bowel function.

General Condition.—Twenty-five cases were classed as "ill" or "very ill"; nine had a good general condition.

Tongue.—In 28 cases the tongue was dry.

Tenderness and Rigidity.—This was maximal in 33 cases.

Site of Tenderness and Rigidity.—Generalized in 19 cases, epigastric only in nine cases, right hypochondrium and right iliac fossa in three cases, epigastrium and right iliac fossa in one case, right iliac fossa only in one case, and right hypochondrium only in one case.

Liver Dullness.—This was lost in 15 cases, impaired in 10, and normal in nine.

Bowel Sounds.—These were present in 21 cases and absent in 13.

Evidence of Other Acute Disease was absent in all cases.

From these findings the following points might be considered as being those in whose absence nothing more than a tentative diagnosis of gastro-duodenal perforation should be postulated: male patients only; temperature, pulse, and respiration not far from normal; previous history of dyspepsia; recent exacerbation of dyspeptic symptoms; sudden onset; onset during waking hours; duration of less than 12 hours; no history of trauma; epigastric or generalized pain; no history of diarrhoea; dry tongue; maximal tenderness and rigidity; generalized, epigastric, or right-sided tenderness; no evidence of other disease.

The value of many of these clinical features is well known. Strang and Spencer (1950) found that more than 90% of their cases gave a history of dyspepsia and over 70% had an exacerbation of symptoms immediately before the perforation. Jamieson (1947) found that in his series of cases perforation at night was rare. He further reports that "severe exertion plays little part in precipitating perforations."

The longest acute history of this series was fourteen hours. Cases of much longer duration have been reported. Beattie (1951) describes four cases with an acute history of over 20 hours, but it seems that since the National Health Service, with the financial anxiety of illness removed, patients call their doctor far more readily.

X-ray diagnosis has not been considered in this series, as in many instances it was not available, and often the patient had too much pain to co-operate sufficiently if it had been available. Stead (1951) discusses the difficulties encountered in *x*-raying patients before reaching a diagnosis. He demonstrated free gas in 38 out of 47 cases, and in 10 cases treated conservatively radiography was either not available or failed to demonstrate gas.

In diagnosing the cases of "acute peritoneal irritation not of gastro-duodenal origin" nine of them closely resembled gastro-duodenal perforations. These case histories are summarized below.

Case Histories

Case 31.—Male aged 15. No previous dyspepsia; sudden onset of epigastric pain, persisting for 12 hours. No vomiting; constipated. Examination: General condition very ill. Tongue dry. Abdomen tender and rigid all over; normal liver dullness; no bowel sounds. P.R.: N.A.D. T., P., R.: 100° F. (37.8° C.), 100, 25. Diagnosis: Widespread peritonitis due to a perforated appendix, the caecum being completely undescended and in the midline. Differential diagnosis: Distinguished from gastro-duodenal perforation by absence of dyspepsia.

Case 33.—Male aged 56. No previous dyspepsia, but abdominal discomfort for seven days, followed by sudden severe generalized abdominal pain, persistent for 48 hours.

No vomiting; normal bowel function. Examination: General condition—very ill. Tongue dry. Abdomen tender and rigid all over; normal liver dullness; no bowel sounds. P.R.: N.A.D. T., P., R.: 97.6° F. (36.4° C.), 120, 24. Diagnosis: Intraperitoneal rupture of appendix abscess causing widespread peritonitis. Differential diagnosis: Distinguished from gastro-duodenal perforation by absence of dyspepsia; a duration of acute history of 48 hours.

Case 38.—Female aged 38. No previous dyspepsia. Sudden onset of generalized abdominal pain while pushing a garden roller. Pain had persisted for 48 hours. No vomiting; normal bowel function; no upset of menstruation. Examination: General condition—good, but slight pallor. Tongue moist. Abdomen tender and rigid all over; normal bowel sounds; normal liver dullness. P.R. and P.V.: No abnormality. T., P., R.: 98° F. (36.7° C.), 100, 20. Diagnosis: Haemoperitoneum due to ruptured tubal pregnancy. Differential diagnosis: Differentiated from gastro-duodenal perforation by sex, no previous dyspepsia, duration of acute history, trauma.

Case 44.—Female aged 36. No previous dyspepsia. Sudden onset of generalized abdominal pain when her husband and she fell and he landed on her abdomen. Pain had persisted for four hours. No vomiting; normal bowel history; normal menstrual history. Examination: General condition—ill. Tongue dry. Abdomen tender and rigid all over; normal liver dullness; normal bowel sounds. P.R. and P.V.: N.A.D. T., P., R.: 99.7° F. (37.6° C.), 94, 30. Diagnosis: Intraperitoneal rupture of serous ovarian cyst. Differential diagnosis: Distinguished from gastro-duodenal perforation by sex, no previous dyspepsia, trauma.

Case 41.—Male aged 21. Previous dyspeptic history suggestive of chronic duodenal ulcer. Slight abdominal pain for 24 hours following a kick while playing football. Sudden onset of severe epigastric pain after this, persistent for 12 hours. No vomiting; bowels constipated. Examination: General condition—ill. Tongue dry. Abdomen tender and rigid in upper part; liver dullness normal; absent bowel sounds; slight abdominal distension. P.R.: N.A.D. T., P., R.: 100° F. (37.8° C.), 110, 20. Diagnosis: Haemoperitoneum due to rupture of liver (lacerated concave surface). Differential diagnosis: Distinguished from gastro-duodenal perforation only by the presence of trauma.

Case 45.—Female aged 48. Several attacks of epigastric pain at intervals of about one month or more, each lasting several days and then subsiding. She had suffered from this form of dyspepsia for several years. Sudden onset of epigastric pain, persistent for 12 hours. No vomiting; normal bowel function. Examination: General condition—ill. Tongue dry. Abdomen tender and rigid all over; normal liver dullness; normal bowel sounds. P.R. and P.V.: N.A.D. T., P., R.: 98.4° F. (36.9° C.), 88, 24. Diagnosis: Widespread peritonitis due to perforated jejunal diverticulum situated 2 ft. (60 cm.) from duodenal-jejunal junction. Differential diagnosis: differentiated from gastro-duodenal perforation only by sex.

Case 67.—Male aged 57. Indigestion for four months—epigastric pain and vomiting. For seven days symptoms much worse and accompanied by sensation of food sticking at lower part of chest. Sudden onset of generalized abdominal pain eight hours before admission; persistent. Vomited since onset. Bowels constipated. Examination: General condition—ill, with marked weight loss. Tongue dry. Abdomen tender and rigid all over; no mass palpable; diminished liver dullness; no bowel sounds. P.R.: N.A.D. T., P., R.: 99.8° F. (37.7° C.), 120, 24. Diagnosis: (1) Widespread peritonitis from perforated appendicitis. (2) Carcinoma of cardia of stomach. Differential diagnosis: Indistinguishable from perforated peptic ulcer.

Case 68.—Male aged 51. Partial gastrectomy 15 months previously for peptic ulcer. Recurrent attacks of epigastric pain for three months. Sudden onset of severe generalized abdominal pain three hours before admission; persistent. Vomited since onset. No bowel upset. Examination: General condition—ill. Tongue dry. Abdomen tender and rigid all over; no mass palpable; no loss of liver dullness; no bowel sounds. P.R.: N.A.D. T., P., R.: 100.2° F. (37.9° C.), 106, 18. Diagnosis: Peritonitis due to perforated carcinoma of descending colon. Differential diagnosis: Indistinguishable from perforated stomal ulcer.

Case 69.—Male aged 75. Vomiting for about one month before admission; no previous abdominal pain. Recent loss of weight. Sudden onset of abdominal pain 12 hours before admission; pain persistent; vomited once. No bowel upset. Examination: General condition—very ill; marked weight loss. Tongue dry. Abdomen tender and rigid all over; distended; no mass palpable; loss of liver dullness; no bowel sounds. P.R.: N.A.D. T., P., R.: 100° F. (37.8° C.), 90, 20. Diagnosis: Widespread faecal peritonitis due to spontaneous perforation of the pelvic colon. Differential diagnosis: Indistinguishable from perforated peptic ulcer.

Comment on Above Cases.—It will be seen that, after rigidly applying the diagnostic screen already described, three cases remain that might easily be diagnosed wrongly as gastro-duodenal perforation (Cases 67, 68, and 69). Case 45 is distinguished only by sex, Case 41 only by the history of trauma, and Case 31 only by the absence of dyspepsia.

Results

Although this paper is primarily concerned with diagnosis, it is obvious that a diagnosis confirmed by laparotomy is worthless if the laparotomy adversely affects the patient's survival. On the other hand, a laparotomy delayed by a mistaken diagnosis in a case in which its necessity is urgent is equally undesirable.

The results in the cases of gastro-duodenal perforation and in those of acute peritoneal irritation from other causes are dealt with. Among the perforations there were no deaths attributable to the laparotomy, but three subsequent deaths were noted (see below).

With the following exceptions all cases made satisfactory recovery after simple closure of the perforation.

Case 18.—Male aged 70. Perforated pre-pyloric ulcer, immediate subtotal gastrectomy: section later proved to be non-malignant. Alive and well, having been followed for three years.

Case 21.—Male aged 54. Perforated carcinoma of the stomach: unfit for immediate gastrectomy; simple closure only. Laparotomy 14 days later revealed peritoneum full of metastases. He died four weeks later.

Case 22.—Female aged 50. Perforated carcinoma of the stomach infiltrating transverse mesocolon; immediate subtotal gastrectomy and transverse colectomy. Died at home suddenly three months after her discharge from hospital (? cerebral thrombosis).

Case 23.—Female aged 29. Perforated carcinoma of stomach, immediate subtotal gastrectomy. Patient alive and well, having been followed up for 12 months.

Case 54.—Male aged 73. Perforated duodenal ulcer. Died on seventh post-operative day from myocardial degeneration and uraemia (300 mg. per 100 ml.) following a violent haematemesis on the fourth post-operative day.

Case 55.—Male aged 70. Perforated carcinoma of pyloric antrum (inoperable). Perforation closed and gastro-enterostomy performed. Alive and well, having been followed up for 6 months.

Among the other cases there were four deaths.

Case 42.—Male aged 79. Ruptured spleen. Died on the table from cardiac arrest.

Case 43.—Male aged 77. Ruptured left gastric artery. Died seven days later from purulent bronchopneumonia.

Case 46.—Male aged 60. Multiple chromaffinomata of small bowel (perforated). Died from leaking anastomosis at the suture where enterectomy had been performed.

Case 47.—Male aged 73. Inoperable perforated carcinoma of caecum. Died five days later from peritonitis, drainage only having been done.

Discussion

Comment on this investigation is centred on four points. (1) Despite careful screening of 36 cases of acute peritoneal irritation from non-gastro-duodenal causes, three remain indistinguishable from gastro-duodenal perforations. In this series, which is too small to be statistically significant, for every 11 true perforations there occurred one case requiring immediate laparotomy, the clinical features being exactly similar to those of a perforated peptic ulcer. Therefore the conservative method of treatment applied to this series would have suffered from a 10% diagnostic error despite rigid selection, and a correspondingly greater error with rigid selection.

(2) It must be considered that the results by the non-operative method may be so vastly superior to those by the operative method that this small diagnostic risk should be accepted. This is not so. Hermon Taylor (1951), Stead (1951), and Beattie (1951) all quote at least one death in their respective series which would not have occurred under operative approach. There were no deaths among the small series of perforations reported here that were attributable to the laparotomy.

(3) The "poor risk case" must be considered. The above authors all report a satisfactory outcome to such cases, which would almost certainly have been fatal if subjected to laparotomy. Here they are on very firm ground in accepting the small risk of a mistaken diagnosis in a patient whose clinical features are typical of gastro-duodenal perforation, but who is a poor risk for laparotomy.

(4) The results of the cases of non-gastro-duodenal origin show that the fatality rate is nowadays small when laparotomy is not unnecessarily delayed. It is wrong to assume that a case will benefit by the delay which results from the mistaken application of the conservative measures for perforations, although some pre-operative treatment is often desirable in these cases. It is also wrong to assume that a patient with perforation of the large bowel would have died in any case.

The final conclusion must be that when a case is diagnosed as a gastro-duodenal perforation it should be treated by laparotomy unless the risk of the operation is thought to be greater than the risk of a mistaken diagnosis.

Summary

Seventy cases of acute peritoneal irritation are presented.

The clinical features of perforated gastro-duodenal lesions are evaluated, and a "diagnostic screen" is described.

The case of peritoneal irritation from all causes are tabulated, and details are given of those non-gastro-duodenal cases in which differential diagnosis was a problem.

The results of treatment are given.

It is suggested that laparotomy be performed on all cases diagnosed as gastro-duodenal perforation if the patient is fit for the operation, and the conservative method be reserved for those cases in which laparotomy would be a serious ordeal.

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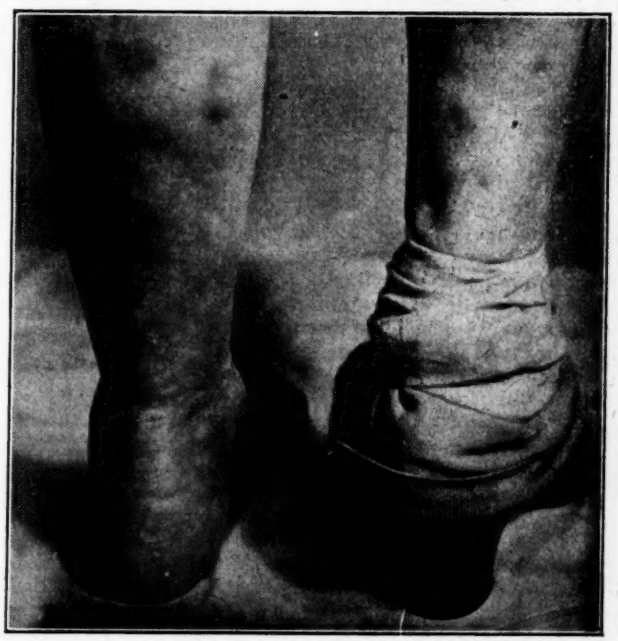
Medical Memoranda

Weber–Christian Disease: Relapsing Febrile Nodular Non-Suppurative Panniculitis

Panniculitis by definition means inflammation of adipose tissue. Parkes Weber (1925) reported one case in which this happened in various areas of the body and caused pain and discoloured swellings of the skin. He examined a nodule microscopically, and reported his case under the heading of "Phagocytosis of subcutaneous fat cells by macrophages." There was no enlargement of the lymph nodes. Christian (1928) reported a similar case in greater detail, adding that fever also occurred. No organisms were found in either case. Despite intensive investigations no cause was discovered for this condition. Alice Carleton (1949) added a further example of this interesting disease to the fifty or so cases in the literature. A further case is now reported, showing the characteristic lesions, relapses, and histopathology.

Case Report

A married woman aged 65 was admitted to hospital as a case of coronary artery thrombosis. A history of breathlessness on exertion, choking sensation, and swelling of the ankles was given, which had been intermittently present in the previous six years. An electrocardiogram revealed no definite myocardial infarction. Concurrently, the patient stated that she had been troubled with small painful swellings of the legs. These became red, did not break down, and after three weeks disappeared. These swellings had appeared in both legs and in both arms. The pain had been severe enough to cause loss of sleep. At the time of admission several such swellings were present, one of which, at the region of the right elbow, was removed for histopathological examination. The swellings recurred at irregular intervals, affecting the legs and arms indiscriminately. After recovery from particularly large and painful swellings a dimple resulted in the skin (see illustration).



The patient has been seen over a period of 18 months, and in that time has had several recurrences of nodules. On May 19, 1952, she was again examined and a large crop of lesions was seen, affecting both lower legs, three smaller lesions being present in the left forearm, and one on the palmar aspect of the right wrist. The lesions were variable in size, some were visible as purplish-red areas which on palpation could be identified as discrete nodules. Others

were palpable only. The distribution of the lesions was asymmetrical. There were none on the face, back, or neck, and there has been no evidence of suppuration. A low-grade pyrexia was present during each observed attack, but the general health has been moderately satisfactory.

The history, together with the typical lesions and characteristic microscopical appearances, confirms the diagnosis. Photographs were shown to Dr. Parkes Weber, who considered the appearances to be consistent with this diagnosis.

Histological examination revealed necrosis of the subcutaneous fat. The epidermis was intact and normal. The subcutaneous fat showed extensive foci of necrosis of the fat cells, these areas being replaced by groups of lipoid-filled phagocytes. Some giant-cell reaction was seen, together with lymphocyte infiltration.

I am indebted to Dr. Alexander Smith, medical superintendent, Stonehouse Hospital, for permission to publish this case.

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Lymphosarcoma of the Appendix

Since Kundrat (1893) first described lymphosarcoma of the appendix many different names have been used to describe this condition. Ewing (1939) endeavoured to clarify the position by stating that lymphoid tissue contained three cellular elements—namely, lymphocytes, reticulum cells of the pulp and follicles, and endothelial cells of the pulp and cavernous sinuses. Thus he maintained that there were two possible types of sarcoma—a malignant lymphocytoma and a reticulum-cell sarcoma.

Lymphosarcoma can appear in the tonsils, lymph nodes, spleen, and thymus gland, and to a less extent in the lymph follicles of the gastro-intestinal tract. Geschichter (1935) stated that sarcoma comprises 3% of all malignant growths of the gastro-intestinal tract—mostly lymphosarcoma. In his series of 46 lymphosarcomata 13 were in the stomach, 20 in the ileum, 10 in the caecum, 2 in the rectum, and 1 in the duodenum.

Our patient had a lymphosarcoma of the appendix, and we record the case to draw attention to the possibility of misdiagnosis as chronic appendicitis, which is so frequent and which may give rise to a false sense of security.

CASE REPORT

A man aged 38 was seen on May 17, 1950. He had a 10-year history of intermittent diarrhoea and vague abdominal discomfort, which during the last 12 months had become a more definite pain localized to the right iliac fossa. Examination revealed no abnormal finding except tenderness localized to the lower pole of the distended caecum. A magnesium sulphate barium meal examination on May 24 showed that the appendix failed to fill.

He was admitted to hospital on August 30. Routine questioning revealed that the pain in the right iliac fossa was a sporadic dull ache which occasionally radiated to the left side of the abdomen. During the previous month his appetite had diminished and his abdomen had become "swollen and tender." His bowels were regular, with a slight tendency to loose motions, during which the pain was accentuated. The pain was relieved by rest and codeine. His only relevant past history was migraine since the age of 16 and glandular fever at 32. His weight was 8 st. 8 lb. (54.4 kg.) and his temperature and full blood count were normal. Chest radiography revealed only a calcified focus at the left apex. On the day before admission the symptoms of pain and nausea became prominent, and it was thought that an acute attack might be supervening.

An operation was performed on September 1. Through a gridiron incision a bulbous-ended pear-shaped appendix 2¼ in. (5.7 cm.) long was found lying retrocaecally, with a hyperaemic base and a similarly hyperaemic caecum. The appendicular mesentery was thick, contained much firm fat, and was extremely vascular. On the serous surface of the organ there was a purplish discoloration close to the base, which was attributed to the local necrosis in the appendix. Post-operative convalescence was uneventful, and the patient was discharged on September 10. Section of the appendix showed replacement of the mucosa and submucosa by masses of lymphoid cells with penetration of the muscle coat in one area. The appearances were those of lymphosarcoma.

During the following 10 months he was seen on eight occasions by both of us. In November, 1950, his weight was 9 st. 4 lb. (58.9 kg.). His appetite has been good, his bowel action normal, and he has been in full active employment. The only clinical finding has been a slightly tender boggy caecum, without any lymphatic glandular enlargement. A barium meal examination and blood count were normal at this time and also in February, 1951. It is significant that tenderness in the right iliac fossa over what might be described as a thickened caecum and a fatty mesentery was still present. This tenderness does not seem to alter. In November, 1953, the patient was still in good health.

COMMENT

Charache (1934) reported a case of primary leiomyosarcoma of the appendix. He summarized 22 reported cases of sarcoma of the appendix. Every one of these cases was diagnosed only on histological section. Clinically the diagnosis was an appendicitis of one kind or another, and the cases were reported only because of the rarity of the lesion. Most of these 23 patients were in the first or third decade of life. The symptoms in all instances were referable to the right iliac fossa, but their duration varied between four weeks and a year, although in two cases there had been symptoms for 10 and 13 years. The occurrence of "attacks" was noticeable in seven cases, whilst in all but two of the remainder the attack persisted for several weeks or presented as acute appendicitis. One case was an incidental finding at necropsy in a man aged 55 who had died of cerebral haemorrhage. Bizard *et al.* (1938) recorded a case of a 27-year-old man who had a lymphoblastic sarcoma; a three-year follow-up showed that the patient was still well. Knox (1945) described a further case in a boy aged 4, a 15-months follow-up recording that the patient was then essentially asymptomatic.

In our patient an interesting feature was the 10-year history of vague and repeated abdominal upsets. Is it that the repeated subacute attacks of appendicitis had slowly altered the structure of the lymphoid tissue and that a gradual change took place from an inflammatory reaction to a state of malignancy? The attack of glandular fever is of particular interest: had it any influence on the presumed development of the sarcomatous change? Other questions may be asked. How many appendices are removed and never sectioned? What is the true incidence of sarcoma in the organ? Is a right hemicolectomy the correct treatment, or local excision followed by radiotherapy?

The prognosis seems to be about seven months. Three years is the longest period of freedom from recurrence that has so far been recorded.

Our grateful thanks are due to Mr. R. Vaughan Hudson, senior surgeon, Middlesex Hospital, for permission to publish this case; to Professor R. Scarff, director of the Bland-Sutton Institute of Pathology, for the section report; and to Sir Harold Graham Hodgson, director of the *X*-ray Diagnostic Department.

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Reviews

JOSEPH BARCROFT

Joseph Barcroft, 1872–1947. By Kenneth J. Franklin. (Pp. 381; 61 plates. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1953.

Your reviewer took this book with him on a visit to the United States and Canada. Wherever it went (and it will do the same in many other countries) it recalled affectionate memories and stories of J. B., of his humanity, gaiety, and wit, of his scientific skill, persistence, and imagination. Dr. Franklin had special qualifications for writing it, not only by his facility in historical studies (physiologists the world over are grateful to him for his history of the physiological congresses, prepared for the Zurich meeting in 1938), but also by his long association with Barcroft's work on foetal circulation. Franklin has tapped many sources and drawn on memories or photographs by many friends for his material; but largely also on the diaries and records of Lady Barcroft, J. B.'s perfect partner, to whom "with admiration and affection" the book is justly dedicated. It is faithful in fact and emphasis, as befits its author's scholarship, but it is a tribute also of world-wide admiration and affection for its subject.

Starting with the Barcroft family in Lancashire in the thirteenth century and in Northern Ireland from the seventeenth, Franklin brings us in Chapter II to The Glen at Newry, Co. Down, where J. B. was born, and from where he learnt his love of boats, sailing in sight of the Mourne Mountains in Carlingford Lough. Thence in Chapter III we are led to Cambridge, where for fifty-five years his life was based. Chapter IV deals with the fruitful period which includes his first expedition to high altitude (Teneriffe). Chapter V covers the second such expedition (Monte Rosa) and the publication (1914) of *The Respiratory Function of the Blood*. It contains the story of J. B.'s part in the first German war, starting with the use of chlorine in the second battle of Ypres in 1915, and mentions the characteristic reply to Quaker friends, "I thought of the parable of the Good Samaritan and obviously I did not want to pass by on the other side." The side he took led to courageous experiments on himself and to a continuing association, lasting into the second German war, with methods and problems of chemical warfare and defence. Could not a Quaker be an Irishman, too?

Chapter VI contains the account of J. B.'s experiments at Cambridge under reduced oxygen pressure and of his third expedition to high altitude (Peru). Few achievements are due to one man only, but the knowledge which gave conviction that oxygen should be used in the final assault on Everest can be attributed as much to J. B. as to any other man. How glad he would have been to hear of its success. Chapters VII and VIII deal with the period of his professorship at Cambridge, Chapters IX to XI with the 10 years, no less fruitful, after he had "retired." Then comes a list of his publications (some 400 of them) mostly jointly with colleagues. He had a remarkable capacity for setting other people to work.

The book is illustrated with many attractive photographs, most of them informal, of J. B. and his colleagues, including a supremely good one of him lecturing in 1935 (Plate 49). These may mean less to those who did not know him personally, but they will add very greatly to the pleasure and interest of his friends.

A reviewer would not be treated seriously if he found no mistakes. In what sense (p. 286) had Japan been "our enemy" since July, 1941? And it is well known to his friends how Dr. D. P. O'Brien celebrated the attack on Pearl Harbour at the Athenaeum Club, not in America; while Houssay's initials are B. A. and not A. E. Apart from these, your reviewer has no complaints.

A. V. HILL.

THE CANADIAN MEDICAL SERVICES

Official History of the Canadian Medical Services: 1939–1945. Edited by W. R. Feasby, B.A., M.D. Volume 2: Clinical Subjects. Published by Authority of the Minister of National Defence. (Pp. 537; illustrated. $5.) Ottawa: Edmond Cloutier. 1953.

The official history of the Canadian Medical Services is to comprise two volumes, the administrative and the clinical. Though issued first in time, this account of the clinical subjects is to form the second of the two volumes. It is published earlier because, as the editor wisely states, "If any useful medical knowledge were to be shared with others as a result of a war, it was felt that it should be set forth as quickly as possible."

This volume not only deals with both medicine and surgery, but it gives four chapters to research carried out in the Services, and no less than a quarter of the book is devoted to statistics. In order to cover such a wide field within a relatively small compass "the accounts leave out the usual details and touch only on the subjects which were new and in which advances were made." This has the advantage that the reader can quickly learn the main lessons of the war, but probably many would have liked a little expansion of some of the articles. Some articles are signed, some unsigned; in the latter the opinions expressed are for the most part authoritative and the result of consultation between experts. It is interesting to note that orthopaedic surgery was not recognized as a separate specialty by the Canadian Army, and a statement is made which might well provide matter for discussion: "No one can say that it would have been better if this specialty had been recognized." There is a good account of the discovery and development of penicillin and of the important part played by the Connaught Research Laboratories in the large-scale manufacture of that substance. We should have liked to see the pioneer work of Guttmann mentioned in the section on rehabilitation of spinal cord injuries. The editor is to be congratulated on the way in which he has marshalled the material at his disposal. The book is well produced.

ZACHARY COPE.

LONG-TERM DIABETES

Long-Term Diabetes: The Clinical Picture in Diabetes Mellitus of 15–25 Years' Duration, with a Follow-up of a Regional Series of Cases. By Knud Lundbaek. Ophthalmological Section in collaboration with Professor V. A. Jensen, M.D., Copenhagen. (Pp. 197; illustrated. 32 Danish crowns.) Copenhagen: Einar Munksgaard. London: Lange, Maxwell and Springer. 1953.

Since the discovery of insulin in 1922, diabetics have lived longer, and it is only in recent years that it has been possible to assess the various complications which may develop in diabetics of many years' standing. "Long-term diabetes," as Knud Lundbaek calls it, is an important syndrome, and by its study much can be discovered and a greater understanding obtained about the fundamental disorders in the syndrome of diabetes.

This book enumerates the findings of exhaustive examination in a follow-up of 165 live and 69 dead diabetics, who had had diabetes 15 or more years, and who had resided in a Danish municipality of about 115,000 people some time during the years 1924 to 1950. Every abnormality and complication occurring in this series of cases has been carefully recorded and discussed under its appropriate heading of disorder or system affected. Each has been preceded by a very complete review of the world literature on the subject, with no fewer than 309 references, covering the whole field of research in these subjects.

Such a detailed analysis must, of necessity, make for heavy reading, but the completeness of the work compensates for this. The bibliography alone is useful, quite apart from the extremely interesting results, which are much in accord with the views of other workers elsewhere. The observations are sound and the conclusions fair and reasonable, none being extravagant. Although not for the student,

this book should prove of value and interest to all those interested in the study of diabetes. Every possible long-term complication of diabetes is carefully described and its incidence recorded. The book is an excellent, painstaking piece of work.

JAMES ROBERTSON.

CONGENITAL HEART DEFECTS

Congenital Abnormalities of the Heart and Great Vessels. By Maurice A. Schnitker, M.D., F.A.C.P. (Pp. 306. £3 3s.) London: Oxford University Press (Geoffrey Cumberlege). 1953.

There is much to commend here. But one may first of all deplore the small number of illustrations. Some of those which should enliven the development of the heart are sure to obscure it, particularly figures 5 and 6; the formation of the interatrial septum should be well and clearly shown. To make up for this the pictures of aortic abnormalities are good, and the lack of diagrams showing development of the heart is not felt so much because the account is so clear; it is indeed one of the best I have read. There is a very good chapter on cyanosis and also finger-clubbing. The section on the use of the cardiac catheter is clear and practical, the objects and the risks being well set out. The author describes the various types of lesion in the traditional three groups of acyanotic, late cyanotic, and cyanotic; perhaps it is time for a new and better classification, but in any case many would question whether defects of the aorta should come under the cyanotic type.

The bronchial arteries get very little attention and are not listed in the index. There is not one *x*-ray photograph. This is a serious fault, for the evidence given by the skiagram on the flow of blood to the lungs is important. Pulsation of the hilar vessels needs more consideration. The point that will interest most readers is the part played by surgical measures in alleviating these defects. This is well and sensibly described. Apart from the omissions mentioned above, this book reads well and provides a clear and up-to-date presentation of the subject.

TERENCE EAST.

MONGOLISM

Mongolism: A Clinicogenealogical Investigation Comprising 526 Mongols Living on Seeland and Neighbouring Islands in Denmark. By Jakob Øster (Pp. 206. Danish Kr. 21. U.S. $3.) Copenhagen: Danish Science Press. 1953.

This monograph is one of the series of clinical and genetic studies of individual abnormalities that are coming from the Institute of Human Genetics at Copenhagen. Like all these monographs, it is a thorough study based on large numbers. In this case over a thousand mongols were ascertained in three counties of Denmark between 1929 and 1949, and 562 were still alive. No definite new conclusions about mongolism emerge from the study, but even so the work has considerable interest.

The incidence of mongolism is put at about 1 in 600 births. The diagnosis can be made only by finding that a child has several of the signs which are common in mongolism. The author's table of the frequency with which different signs were found is most instructive. He notes, however, that even if one takes the ten best signs there are still children with only two or three of them who are indubitably mongols. The book appears to have been written in 1951, and the author did not use Penrose's useful contribution of a precise method of measuring the abnormality of the dermal ridges of the palms. The author includes mental deficiency in his criteria for diagnosis and so side-steps the interesting point whether an occasional mongol may have average or even above-average intelligence.

It is agreed that there is no specific treatment but that every effort must be made to educate the child to make the best social adjustment it can. In discussing aetiology the author notes the usual finding that mongols become commoner as the mother gets older. He also found that the interval before and after the birth of a mongol child is unduly long when compared with intervals before and after births of the same order in other families where there is a mongol. But he does not appear to have allowed for the effect of maternal age on fecundity or the natural reluctance of a mother to start another pregnancy after the birth of a mental defective. There was no consistent history of maternal disease early in the pregnancy which gave rise to a mongol. There was, too, only a low incidence of mongolism among the brothers and sisters of mongols. Unfortunately, in contrast to the usual practice in monographs from the Copenhagen Institute, the sibships are not set out in detail except for the five in which a sib is also a mongol and the one in which a half-sib is also a mongol; and the section discussing the sibships is confused and perhaps mistranslated. It appears that 6 of the 354 children born alive after a mongol were also mongols. It is not stated which was the index case in these sibships, but, even if the first mongol in the sibship was always the one ascertained, this gives a low proportion of subsequent children affected, perhaps not significantly greater than the chance expectation. The references given at the end are very comprehensive up to 1951, and the list will be welcome to all who study mongolism.

C. O. CARTER.

CLASSICS IN DERMATOLOGY

Classics in Clinical Dermatology: With Biographical Sketches. By Walter B. Shelley, M.D., Ph.D., and John T. Crissey, M.D. Introduction by John H. Stokes, M.D. (Pp. 485; 111 illustrations. 75s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

It is always pleasant and profitable to live with the masters both old and new. This is particularly true for the clinician, whose masters are those men whose ability, curiosity, and observations, combined with lucid exposition, have done most to advance the art of clinical medicine. The authors of this volume present pertinent extracts from about 150 original papers from 90 eminent dermatologists past and present. They divide the contributions into four periods, the early and middle periods, a golden age from Duhring to Caesar Boeck, and finally more recent observations from such masters as Brocq and Darier, Jadassohn and Bloch, Fox and Parkes Weber. A brief but adequate biographical note on each master precedes the extracts from original contributions, and it is not difficult to get a picture of the man as well as an accurate account of his observations. The abstracts are meant to reflect the enthusiasm and temperament of the authors. The book starts with the observations of Robert Willan, a Yorkshireman and the father of dermatology, and ends with those of John O'Brien, an Australian and perhaps dermatology's youngest son.

Dr. Shelley and Dr. Crissey must have derived great satisfaction as well as instruction from these researches, and dermatologists will be grateful for this easy and useful work of reference. The authors do not pretend that it is a complete account of all the great names in dermatology, as indeed it is not, though it is well proportioned and a valuable addition to the history of dermatology.

It is to be hoped that further editions may enlarge the work. It would be interesting to read Civatte's description of poikilodermie beside the excellent report of Riehl's melanosis, and to find such names as Sabouraud, Rasch, Haxthausen, and Whitfield in the list, to name only a few who would further enrich the book.

It is well and attractively produced on good paper, with hardly a printing error. There are more than 100 illustrations of dermatologists and of the affections they describe. The literary value of the contributions, especially of the older masters, is in such contrast to that of much modern medical literature that students might well be directed to the book for this as much as for its historical interest.

J. T. INGRAM.

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CORTISONE AND INFECTION

Cortisone has moved with astonishing speed from pharmacological curiosity to therapeutic stand-by, and much is now known about its secondary ill-effects. In the course of treatment they need constant attention. The most important of them in practice is the drug's tendency to promote infections. This action is as difficult to understand as some of its therapeutic actions. Now a useful review of the evidence comes from Lewis Thomas,[1] of the University of Minnesota, and not the least important part of it is his demonstration that several apparently obvious explanations fail to fit the known facts. The most notable fact is the width and non-specificity of the action. We are used to antibiotics of wide range, but no drug has a range of favourable action at all comparable to cortisone's range of unfavourable action. It seems that, whenever cortisone has been administered to a vertebrate host parasitized by an invertebrate, the course of events has been altered to the detriment of the host. This may be obscured by the symptom-masking effect of the drug, so much so that some of the earlier publications reported clinical improvement.[2 3] These were soon shown to be illusory, and it is now fairly well established that all the common bacterial infections are enhanced, including those with spirochaetes and the tubercle bacillus. The effect is the same with viruses, a fungus,[4] and protozoa. The effect on helminths remains slightly doubtful, though a clear answer to the disputed effect[5] in trichiniasis seems to have come from Stoner and Godwin,[6] who found increased susceptibility in mice. So far as the host is concerned, cortisone has been shown to promote infections of one sort or another in man and all the ordinary experimental mammals, though the only non-mammalian host for which any data are available is the chick embryo.

This striking breadth of effect might be compared to that of gross malnutrition or of sublethal doses of whole-body irradiation, but these both produce many diverse changes in the host: cortisone enhances all infections in an otherwise fit animal. This suggests that the defence mechanisms of the body, which often seem so diverse in combating different parasites, all have something in common—that the tree has a single trunk to which cortisone lays the axe. Thomas examines six mechanisms by which cortisone might possibly act, on the worthwhile assumption that only one is needed to account for all the various manifestations. He first considers the possibility of a direct action on the organisms. For this there is no experimental evidence, and *a priori* it is improbable that any single substance would directly stimulate the growth of so exceedingly diverse a group of organisms. Secondly, he considers the possibility of a direct effect on polymorphs, and this it seems can be as quickly dismissed, for they are not concerned in the defence against most fungus, virus, and protozoal infections. It may be difficult to deny to cortisone some effect on polymorphs, but evidence from many independent studies (Rebuck and Mellinger's[7] is worth special notice) shows that they are the least affected of all the better-known elements of the inflammatory reaction. A third possibility seems plausible at first. The capacity of cortisone to suppress, reduce, or delay the formation of antibodies is well established and applies to a wide variety of antigens.[8–12] Certainly there must be circumstances under which this is important. Yet cortisone enhances virus infections in the chick embryo, in which no antibodies are produced. Again, the effect is often so rapid as to preclude any possibility of involvement of antibody reaction. If, fourthly, we consider the local defence mechanisms, we find ourselves in similar difficulties. Local inflammatory responses are hindered by cortisone,[13] and no doubt this action must sometimes be important, but it cannot account for cortisone's capacity to enhance all infections. Most specifically, it cannot account for the promotion of septicaemia after intravenous injection of organisms, where no local inflammation has occurred. There are several naturally occurring generalized infections in which no stage of local reaction at the point of entry or elsewhere can be

[1] Thomas, L., *Ann. N.Y. Acad. Sci.*, 1953, **56**, 799; see also *Ann. Rev. Med.*, 1952, **3**, 1.
[2] Finland, M., *et al.*, *Proc. First Clin. A.C.T.H. Conf.*, 1950, p. 529.
[3] Smadel, J. E., *et al.*, *Ann. intern. Med.*, 1951, **34**, 10.
[4] Cavallero, C., and Sala, G., *Lancet*, 1951, **1**, 175.
[5] Rosen, E., *Amer. J. med. Sci.*, 1952, **223**, 18.
[6] Stoner, R. D., and Godwin, J. T., *Amer. J. Path.*, 1953, **29**, 943.
[7] *Ann. N.Y. Acad. Sci.*, 1952, **56**, 715.
[8] Germuth, F. G., and Ottinger, B., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **74**, 815.
[9] Fischel, E. E., *et al.*, ibid., 1951, **77**, 111.
[10] Billingham, R. E., *et al.*, *British Medical Journal*, 1951, **1**, 1157.
[11] Robinson, H. J., and Smith, Amelia L., *Ann. N.Y. Acad. Sci.*, 1952, **56**, 756.
[12] Carrère, L., and Roux, J., *Ann. Inst. Pasteur*, 1952, **83**, 26.
[13] Duke-Elder, S., and Ashton, N., *Brit. J. Ophthal.*, 1951, **35**, 695.

traced, and yet cortisone enhances them. Fifthly, various serum components are known or suspected to take part in defence against infection—complement, preformed antibodies, C-reactive protein, hyaluronidase inhibitor, and others. Little relevant is known of most of them, but it is unlikely that any are of importance here.

Finally we come to the sixth hypothesis—a direct effect on the cells of the reticulo-endothelial system. The R.E. system clears particulate matter from the blood, and there is no doubt it plays some part in practically all infections. Critics may object that the details of the local effect remain vague; and it seems, at least to the histologist, that the brunt of the action of cortisone on the lymph nodes and spleen falls on the lymphoid elements rather than on the phagocytic. But here Thomas presents some interesting experiments. If this sixth hypothesis is true, other methods of damaging the R.E. system should have the same effect as cortisone. The only available method—that of "blockade" by overloading the system with injected material—is of doubtful value, but in this case it seems to have been used effectively. Thorotrast and saccharated iron were used as blockading agents. In animals treated with them three close parallels with the effect of cortisone were found. First, both blockade and cortisone interfere with the clearance of particulate matter from the blood, whether the particulate matter is colloidal gold or streptococci. Secondly, both promote the dissemination of streptococci and pneumococci, injected intradermally in doses normally giving rise only to localized infections. Thirdly, both promote the absorption of meningococcal toxin injected intradermally. The first of these effects might well have been expected, but that R.E. blockade should have so striking an effect on local defences and on toxin absorption was *a priori* unlikely and affords strong evidence that cortisone and blockade are acting in the same way. While these experiments seem convincing, independent confirmation is needed. The effect of cortisone on the host–parasite relationship may after all prove to be simply the summation of a number of independent mechanisms concerning antibodies, tissue permeability, phagocytosis, and others, all of which happen to work in the same direction. On the other hand, it may be something more fundamental—a differential effect, perhaps, on the protein metabolism of vertebrates and invertebrates. Even if its effect on the R.E. system is the explanation, many questions remain to be answered. To most people the practical therapeutic problem will seem of chief importance, for a method of preventing the infection-promoting action of cortisone, other than the blunderbuss one of combining it with antibiotics, would be a major advance. Thomas's work opens up at least the possibility of an approach to this.

THE SPREAD OF CANCER

In both Britain and North America, in spite of modern methods of treatment and intensive efforts to secure early diagnosis, breast-cancer mortality rates for defined age groups maintain an almost constant level.[1] The reason for this is that with few exceptions the early dissemination of tumour cells which later produce metastases defeats all forms of local therapy, even when this is applied promptly and efficiently. Metastasis is indeed the sinister shadow hanging over the treatment not only of mammary cancer but of many other kinds of cancer also. The thorough study of metastasis by every possible means—morphological, experimental, and chemical—should therefore be a major part of cancer research. Willis[2] has stressed this view in these words:

> "Elucidation of the chemical and other factors which determine the success or failure of disseminated tumour cells to survive and grow in new sites might assist in the search for effective chemotherapeutic agents. The great series of grafting experiments already performed for us in the dissemination and metastasis of tumours is thus worthy of close study; this should be supplemented by experimental investigations of metastasis."

In the opening pages of this issue we publish Professor G. R. Cameron's Florence Blair-Bell Memorial Lecture. In this he discusses recent work and speculation on the subject of the spread of cancer, with special attention to the high incidence of metastatic tumours in the liver. These are, for most kinds of primary growths, not only more frequent and abundant than metastases elsewhere, but they grow more actively and show higher proportions of cells in mitosis. Abortive tumour embolism, which is often seen in the lungs, is very uncommon in the liver. The "seed–soil" concept of tumour metastasis is thus particularly germane here. Before turning to the liver as a site of metastasis, Professor Cameron broadly reviews the known facts about the invasive properties of tumour cells, and then discusses the various hypothetical factors which may be concerned in rendering a given tissue a fertile or a poor soil for neoplastic growth—blood supply, oxygenation, nutritional properties, possible defence mechanisms,

[1] McKinnon, N. E., *Lancet*, 1954, 1, 251.
[2] Willis, R. A., *Pathology of Tumours*, 1953, 2nd ed., London, p. 206.
[3] Paget, S., *Lancet*, 1889, 1, 571.

metabolic qualities of host and tumour cells, and competition between tumour cells and organ parenchyma.

If, as seems certain, chemical factors are important in the development of blood-borne secondary growths from disseminated tumour cells, the explanation of these will probably come from a study of metastasis in the liver; and to this study histopathologists, experimentalists, and chemists have each their essential contribution to make. There has been a tendency in recent years for some experimentalists to belittle the value of morbid anatomy—"dead-meat" pathology—and to suppose that little remains for it to contribute to knowledge of disease processes. Professor Cameron, himself an expert morbid anatomist as well as an experimentalist, provides here a timely reminder of the mistakenness of this view. His arguments embrace and depend on morphological and experimental data in equal measure and clearly exemplify their interdependence and complementary character. It was morbid anatomical observations, like those early ones of Stephen Paget[3] in 1889, which first pointed to the anomalous distribution of metastatic growths in the body; and it is similar more thorough observations, aided by improved microscopical and staining techniques and by phase-contrast and electron microscopy, which can provide the essential structural basis for progress in our understanding of the fate of disseminated tumour cells in various tissues. It may well be true that pure morphological pathology, unilluminated by controlled experiment, may not be capable of solving these problems, but it is also true that the pure experimentalist may be equally incapable of their solution. It is by a well-balanced union of both disciplines, so well exemplified in Professor Cameron's exposition, that light will be gained on these and many other obscurities in tumour pathology.

SHIVERING

The cold spell has led to embittered reflections on the deficiencies of British thermal engineering, and consoling thoughts about the perfection of the physiological mechanisms that are brought into play when the body is submitted to thermal stresses have brought little comfort. If a naked man lies at rest in a cold environment, certain acts of "physical thermoregulation" immediately come into play, all with the function of reducing the loss of heat from the surface of the body to a minimum. For example, as a result of the constriction of the cutaneous vessels the skin temperature falls and the rates of evaporative, convective, and radiation losses are minimized. The remarkable feature of this response, where man is concerned, is that there is no increase in heat production, so that if these physical adjustments are inadequate to prevent a sustained negative heat balance the whole body cools. When the temperature of the blood has fallen by about 0.5° C., further cooling is arrested by the onset of shivering, a rhythmical, well-coordinated contraction of the voluntary musculature that may increase the total heat production of the body by as much as 400%.

A cat's love of warmth is only too obvious, yet its owner who remorselessly lifts it from the hearth and turns it out for the night in the coldest weather is never worried whether it will catch a chill; his confidence is fortified, moreover, by observing, on its return in the morning, that it is not shivering but only very hungry. The cat, in common with other lower animals and birds, possesses, in addition to its powers of regulating heat loss—physical thermoregulation—a so-called mechanism of "chemical regulation" whereby its metabolism is very delicately adjusted to the thermal demands of its environment. It is presumably this chemical regulation, acting together with restricted heat loss through pilo-erection and vasoconstriction, that permits a cat to withstand such a sudden drop in external temperature without shivering. Man, as we have said, does not exhibit this nice adjustment of his metabolic rate to the environmental demands; instead, mechanisms to restrict the loss of heat (both physiological and artificial, such as the wearing of clothes) have been brought to a high degree of efficiency, and only as a last resort is an increase in metabolic rate invoked—that is, with the onset of shivering.

Shivering therefore appears as a delayed mechanism, only being brought into play when the physical mechanisms restraining the loss of heat from the body have failed to establish a balance of heat production and heat loss at the normal blood temperature; it is thus only one of several physiological mechanisms at the disposal of higher reflex centres concerned with the function of thermoregulation. The neurological aspects of these centres have not been completely elucidated; in lower animals a heat-sensitive centre, stimulation of which leads to vasodilatation, panting, and sweating, has been described in the anterior hypothalamus; stimulation of the lateral hypothalamic area, on the other hand, causes vasoconstriction and pilo-erection, but no shivering. There would thus appear to be two separate reflex centres in the hypothalamus, the one evoked by heat and the other by cold.

The nervous control of shivering, which is not evoked by stimulation of the hypothalamus, is not entirely clear; the other responses to cold are essentially visceral, and it is not surprising that they are under the control of the hypothalamus, a region so closely associated with autonomic function. Shivering is a reflex involving the voluntary musculature, and might be expected to be controlled by centres concerned with somatic activity; according to Beattie and Kerr the centre lies in the caudal half of the medial portion of the thalamus. That the cortex is also involved is

suggested by the work of Aring, who found that primates with lesions in area 4—the somatic motor area—began shivering long before there was any drop in rectal temperature. A lowered blood temperature would appear to be the usual effective stimulus to evoke the shivering reflex; but it may also be evoked by locally applied cold insufficient to lower the blood temperature, and this is presumably mediated by a reflex arc involving, as sensory pathway, the cold receptors and spinothalamic tracts.

The usual concomitants of fear—such as sweating, pilo-erection, vasoconstriction, etc.—may be described as a hypothalamic syndrome released by higher activity, presumably in the frontal cortex. It is interesting that shivering is associated in this complex, because, although it is not a form of autonomic activity, it is released at the same time, thereby showing the close relationship that must exist between the hypothalamic centres of thermoregulation and the thalamic centre controlling shivering. The shivering of fever is only an apparent anomaly: the body temperature is high, but this is a purposive response to an invading pyrogenic agent and would be defeated if the thermoregulatory cooling mechanisms were called into play; instead the warming mechanisms are invoked, among which the most effective is shivering.

THE HAND

In these days of increasingly complex and specialized techniques it is refreshing to be reminded from time to time that good medical practice still depends largely on careful clinical observation. Silverman and Littman,[1] reviewing the value of examination of the hand from the point of view of the cardiologist, have drawn attention to the excessive palmar sweating so often seen in patients with the effort syndrome. Increase in the secretion of sweat from the hand is one of the most constant physical manifestations of emotional tension, a fact made use of in the construction of "lie-detector" machines and similar apparatus used in psychological investigations, and it is a common clinical finding for example in thyrotoxicosis. Pallor of the palm is regarded by many clinicians as more reliable than mucosal pallor as a sign of anaemia, and Wintrobe[2] states that absence of redness in the palmar creases indicates a haemoglobin level below 7 g. per 100 ml. The orange-yellow pigmentation of carotinaemia may be almost confined to the palms and may direct attention to bizarre dietary habits. The cold, harsh, dry hand of myxoedema is well known; more easily missed perhaps is the palmar hyperkeratosis which may reveal chronic arsenical poisoning, particularly when it is accompanied by the typical pigmentation. Of particular interest is the condition sometimes seen in pregnant women and in patients with chronic liver disease—namely, a bright red colour of the palms, usually most intense in the hypothenar eminence and central part of the thenar eminence but sometimes seen also on the palmar surface of the finger-tips, in association with arterial "spiders" over the upper half of the body. It is attributed to the high oestrogen levels which occur in these two conditions.

Cirrhosis of the liver is also one of the less common causes of clubbing of the fingers, one of the oldest of physical signs but still one of the most obscure. An increased peripheral blood flow was found by Mendlowitz[3] in patients with clubbing; and Lovell[4] believes that this leads to an increase in connective tissue, the localization in the distal finger segment being attributed to the predominance there of arterio-venous communications. But the cause of the increased blood flow remains unexplained. The full syndrome of pulmonary osteoarthropathy, which in its early stages is occasionally mistaken for rheumatoid arthritis, is seen most often in patients with bronchial carcinoma and undergoes regression after successful resection of the affected lung. One of the most helpful signs in the fingers is koilonychia, which was shown by Waldenstrom[5] to be usually a direct effect of iron deficiency. Osler's nodes in the pads of the fingers are almost pathognomonic of subacute bacterial endocarditis, but splinter haemorrhages occur quite often also in other diseases, being seen for example in most patients with trichinosis.[6,7] Another disease associated with Osler's name, hereditary telangiectasia, may be suggested in a patient with mucosal bleeding by purplish, round, sharply circumscribed lesions in the finger pads or nail bed; microscopically these are seen to consist of tortuous coils of tiny aneurysmal vessels. Finally, the familiar Heberden's node has recently been given more precise significance by Kellgren and Moore,[8] who regard it as forming part of a constitutional syndrome they have called primary generalized osteoarthritis, which mainly affects middle-aged women and can be distinguished clinically from the degenerative arthropathies.

VIOMYCIN

No antibiotic hitherto discovered is the equal of streptomycin in activity against the tubercle bacillus, but there are certainly two with somewhat less activity which may be turned to practical account. Terramycin has been used in combination with streptomycin on the principle that combined therapy delays the development of resistance, one object in view being to substitute it for P.A.S. in patients intolerant of that drug. The findings of Des Autels[1] in a limited number of cases encourage this policy; after a 120-day course of streptomycin given twice weekly, streptomycin-resistant bacilli were found in 17% of patients also given P.A.S. and in only 5% of those also given terramycin. The other antibiotic of secondary usefulness is viomycin, earlier studies of which have previously been referred to in these columns.[2] This drug has chiefly been used

[1] *New Engl. J. Med.*, 1953, **249**, 839.
[2] *Clinical Haemotology*. Philadelphia. 1951.
[3] *J. clin. Invest.*, 1941, **20**, 113.
[4] *Clin. Sci.*, 1950, **9**, 299.
[5] *Acta med. scand. Suppl.*, 1938, **90**, 380.
[6] McNaught, J. B., *Amer. J. trop. Med. Hyg.*, 1939, **19**, 181.
[7] Houston, J. C., and Ross, L., *Lancet*, 1941, **2**, 397.
[8] *British Medical Journal*, 1952, **1**, 181.

in a different way—namely, as a substitute for streptomycin when bacillary resistance to the latter has developed. In the very unfavourable cases in which it was first tried little benefit was obtained, and a rather forbidding triad of toxic effects was observed—disturbances of the eighth nerve, the kidney, and the plasma electrolytes.

Despite these unfavourable initial findings, and because they could be discounted by the unpromising nature of the clinical material and perhaps by the excessive dosage used, a trial of viomycin was instituted in the Veterans' Administration (U.S.A.) study of the chemotherapy of tuberculosis, the results of which have been described in two reports.[3] [4]

It was decided in the first place to reduce the dose of viomycin to 2 g. twice weekly in the hope of minimizing toxic effects, and on the basis that streptomycin given as infrequently as this has proved effective. The three regimens adopted were viomycin alone and together with either 1 g. streptomycin twice weekly or 12 g. P.A.S. daily, the duration to be at least four months. Of the patients chosen for treatment the great majority had had previous streptomycin treatment and had streptomycin-resistant bacilli: 93% were classified as far advanced and the remainder as moderately advanced; all had cavities and all were sputum-positive at the start of treatment. The drug caused toxic effects in 24% of patients, and in 13% the treatment had to be discontinued on this account. Some clinical improvement was produced in 34%, and moderate or marked improvement in 17%, of the patients on combined regimens. The corresponding figures for viomycin alone were 14% and *nil*. Combination with another drug thus gave clearly superior results, and this difference is also reflected in the numbers of patients whose condition deteriorated during treatment, which were 24% of those on viomycin alone and only 7% on combined treatment. Sputum conversion did not show this difference, occurring in about 15% of each group. Acquired bacillary resistance to viomycin developed to a maximum of about 40% of cases after longer periods of treatment, and was rather commoner in patients receiving this drug alone.

These are not impressive results, but they must be interpreted with due regard to the unpromising clinical material on which they are based. Patients in whom treatment with streptomycin has failed to arrest the disease can naturally not be expected to respond invariably to another and somewhat less potent drug. On the other hand it clearly has a place in the treatment of such patients, provided the disease is not too far advanced. A recent communication from the Ministry of Health states that limited quantities of viomycin will soon be available for use in N.H.S. hospitals only. It is accompanied by a memorandum of instructions for use, advocating the bi-weekly 2-g. dose used in the American study, combined with streptomycin, P.A.S., or isoniazid "as dictated by the drug resistance position."

[1] *Transactions of the 12th Conference on the Chemotherapy of Tuberculosis*, p. 304. Veterans' Administration, Washington. 1953.
[2] *British Medical Journal*, 1951, **1**, 686.
[3] *Transactions of the 12th Conference on the Chemotherapy of Tuberculosis*, p. 300. Veterans' Administration, Washington. 1953.
[4] *Quarterly Progress Report on Chemotherapy of Tuberculosis*, p. 84. Veterans' Administration, Washington. October, 1952.

THE ORGANS OF ZUCKERKANDL

The medulla of the adrenal gland, which contains adrenaline and also a small proportion of noradrenaline, is described as chromaffin tissue because it stains with potassium dichromate. This stain depends on the formation of brown pigments by the oxidation of the adrenaline, and other oxidizing agents give the same stain. It has long been known that chromaffin tissue occurs in the body outside the adrenal gland, and in 1901 Zuckerkandl[1] described the presence of a mass of cells of this kind on the anterior surface of the aorta near the origin of the inferior mesenteric artery. Two years later Kohn[2] showed that these cells originated, like the cells of the adrenal medulla, from the neural crest. This collection of cells on the aorta has since been known as the organ or organs of Zuckerkandl. They are normally not present in the adult, and in 1925 Ivanoff[3] stated that they reach their greatest development in children aged 12–18 months, after which they become fibrosed and atrophic.

West, Shepherd, Hunter, and Macgregor[4] have recently compared the changes which take place during foetal life and after birth in the organs of Zuckerkandl with those in the adrenal medulla, making both pharmacological and histological examinations. Their general conclusion is that the organs of Zuckerkandl are the main site of formation of noradrenaline in foetal life, during which the adrenal medulla is immature. They examined the organs of Zuckerkandl and the adrenal medulla collected from a series of subjects 6–48 hours after death. Histologically the organs are mature at about twenty-two weeks of gestation, and from then do not change until some months after birth. At about 8 months after birth there is a decrease in vascularity and in the size of the cells and an increase in fibrous tissue. The adrenal medulla, on the other hand, begins to develop only after birth. The pharmacological investigation showed that the amount of noradrenaline increased steadily in the organs of Zuckerkandl from 15 weeks up to 2 months after birth, the total being appreciably greater than that in the adrenal medulla during this period. Thereafter the amount in the organs declined and that in the medulla shot upwards.

Perhaps the most important aspect of this work is the indication that tumours of the organs of Zuckerkandl may occur and lead to repeated hypertensive crises in the same way as tumours of the adrenal medulla. These can be successfully diagnosed by the amount of noradrenaline present in the urine. The surgeon who then fails to find an adrenal tumour should inspect the area of the organs of Zuckerkandl. Engel and Euler[5] have already reported one case.

[1] *Anat. Anz.*, 1901, **19**, Erganzungsh. 95.
[2] *Arch. mikr. Anat.*, 1903, **62**, 263.
[3] *Z. Anat. EntwGesch.*, 1925, **77**, 234.
[4] *Clin. Sci.*, 1953, **12**, 317.
[5] *Lancet*, 1950, **2**, 387.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

LABORATORY INVESTIGATIONS IN THE DIAGNOSIS OF IRON-DEFICIENCY AND SIMPLE CHRONIC ANAEMIA

BY

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Iron-deficiency anaemia occurs when the body gains iron more slowly than it should to provide for the needs of growth or to compensate for loss by haemorrhage. Only this factor of iron balance is of importance, so that nutrition enters into consideration only in so far as the food contains iron. Once iron deficiency has been demonstrated the laboratory tests to be used will be those which detect imperfect absorption of iron or loss of iron—that is, bleeding. It is easy to demonstrate iron deficiency, but not so easy to demonstrate its precise aetiology. The diagnosis of iron deficiency is complete only when the relative importance of growth, iron absorption, and blood loss have been assessed and when the site of blood loss is known. Every pathologist has performed necropsies on patients with carcinoma of the colon who had been treated for months for their iron-deficiency anaemia—treated without investigation until their resectable carcinoma had metastasized. It would be, of course, impossible to investigate exhaustively every patient, so the choice of investigation must depend on knowledge of the natural history of iron-deficiency anaemia.

Iron deficiency occurs during the first six months of life in premature infants, whose parasitism on their mother is cut short before they have obtained all the calcium and iron they need: the anaemia is more severe the more premature the birth. Childhood is usually free from iron deficiency, unless nose-bleeds are very severe, or bleeding occurs from peptic ulcer in a Meckel's diverticulum, or a peptic ulcer develops in a hiatus hernia. The menarche may lead after a few years to chlorosis in a young woman whose dietary fads are more extreme than usual; each pregnancy costs the mother at least 300 mg. of iron—a year's absorption from food (and bleeding from peptic ulcer in a hiatus hernia is commoner in pregnant women than in other subjects); and an abortion may cause even greater losses. In the fourth and fifth decades fibroids cause menorrhagia and absorption of iron is less because achlorhydria becomes common. Throughout adult life, in men as well as women, peptic ulceration and piles contribute to anaemia, and from the fifth decade malignant disease of the gastro-intestinal tract must always be considered. There are other causes of blood loss, such as ulcerative colitis, Crohn's regional ileitis, diverticulitis, and tuberculous ileitis, but in these anaemia is rarely the presenting symptom.

Iron deficiency is usually accompanied by some reduction in haemoglobin level, to 12.4 g. (80%) or below, but one occasionally sees anaemic polycythaemia with haemoglobin levels of 100% (14.8 g.) or more, though iron deficient.

Recognition of Iron Deficiency

Estimation of haemoglobin and of packed cell volume allows the calculation of the mean corpuscular haemoglobin concentration (see last week's article in this series, February 6, p. 326); if below 30% this indicates iron deficiency, between 30 and 32% iron deficiency may be present, but it is slight, while over 32% it is absent. The stained film will show anisochromia, and if the anaemia is moderate or severe the cells will tend to be small, misshapen, and to vary excessively in size (microcytosis, poikilocytosis, anisocytosis) while they will contain less haemoglobin than normal (hypochromia). In severe anaemia target cells are often present, and they may lead to confusion with thalassaemia (Mediterranean anaemia or trait), found in Cypriots, Italians, and Greeks, or sickle-cell anaemia or trait, found in Africans and a few tribes of India or Persia, in neither of which congenital peculiarities does iron have any therapeutic value. If it is possible to estimate serum iron, it will be found to be lowered in iron deficiency and normal in the congenital anaemias.

Having established the presence of iron deficiency, one must consider aetiology; and if the history given by the patient clearly indicates a simple cause, such as menorrhagia or addiction to eccentric foods, treatment can be started without delay. If, however, there are no leading symptoms or signs one must first exclude bleeding from the gut.

Gregerson's benzidine slide test is here very useful. Powders of 25 mg. of benzidine and 200 mg. of barium peroxide are dissolved in 5 ml. of glacial acetic acid; a smear of faeces is made on a slide and two or three drops of the reagent added: a blue colour appearing within 30 seconds is presumptive evidence of blood, though this should be confirmed by the standard benzidine or orthotolidine tests after the patient has been on a meat-free diet for three to four days. A positive Gregerson test is not proof of bleeding, but it establishes a prima facie case for further investigation. One should, of course, exclude the presence of bleeding piles before using it, and this necessitates proctoscopy, while in older persons a digital examination may reveal a carcinoma.

Refractory Iron Deficiency

Once the diagnosis is made and the patient given iron and ammonium citrate mixture or ferrous sulphate compound tablets improvement should be rapid: the haemoglobin should rise by 4–20% weekly. If this rise fails to occur, it may be because the patient is not taking the iron or because it is not being absorbed.

Patients, especially women, often fail to take iron tablets because they claim that the tablets give them indigestion, diarrhoea, or constipation. This can be avoided by instructing them to take for one week one tablet in the middle of the main meal of the day; in the second week to add a second tablet in the middle of the next meal; and, thereafter, a third tablet in the middle of the third meal. Alternatively one of the preparations of ferrous gluconate may be prescribed, for there is no doubt that these cause less digestive disturbances than does ferrous sulphate. However, some patients take their tablets religiously without in any way affecting their anaemia, and this is an indication for the administration of iron by vein; it is also an indication for examination of the stools, for many patients who fail to respond to iron by mouth can be shown to have steatorrhoea. The classical method of Holt, Courtenay, and Fales for the estimation of faecal fat, which was performed on an isolated dried specimen, is now less used and is being replaced by methods in which an aliquot of the 24-hour stool is analysed without drying. This change in method reflects the interest in fat balance rather than fat excretion. To-day one expects over 90% of ingested fat to be absorbed and but 10% excreted; any greater excretion is considered evidence of steatorrhoea. If steatorrhoea is present, iron absorption virtually ceases, and steatorrhoea is the com-

monest cause of the finding that an iron-deficiency anaemia fails to respond to iron by mouth but responds rapidly to intravenous iron. Steatorrhoea causes iron deficiency far more often than it does megaloblastic anaemia.

Anaemias Secondary to Other Diseases

The production of red cells may be slowed or their destruction made more rapid by a number of diseases which have no direct association with the blood or bone marrow. Red-cell production is diminished by infection, by nitrogen retention (chronic uraemia) as in chronic nephritis, and by other disease states such as rheumatoid arthritis and myxoedema. That an anaemia may be due to one of these causes should be suspected when a steady or slowly progressing anaemia, usually of moderate severity (haemoglobin over 10 g.) is not due to iron deficiency (normal M.C.H.C.), and the cell volume is near or slightly below the lower limit of normal (M.C.V. 70–85 μ^3), though in myxoedema the cells may be slightly enlarged (macrocytosis, M.C.V. 95–115 μ^3).

In all such anaemias, if the blood count gives no clear indication for therapy a series of investigations may be initiated, each designed to exclude one or other cause. Adequate history-taking and physical examination should exclude the grosser forms of disease such as bronchiectasis, diverticulitis, osteomyelitis, or ulcerative colitis, but a differential leucocyte count showing neutrophilia and a raised erythrocyte sedimentation rate would suggest that a further and more intensive search for a site of infection might be desirable. Some infective processes show minimal changes in leucocyte counts, and of these tonsillitis and subacute bacterial endocarditis are very important; in these the count may be quite normal or there may be slight neutrophilia and lymphocytopenia, usually with some monocytosis, though such changes are inconstant. In typhoid fever (though not in the paratyphoids) and in brucellosis there are neutropenia and monocytosis. Brucellosis occasionally becomes very chronic, causing anaemia with only occasional bouts of fever; in such patients the monocytes may be mistaken for lymphocytes and a diagnosis of lymphatic leukaemia entertained. Fortunately, brucellosis is fairly uncommon in Britain, but agglutination reactions may be worth performing in a patient with an obscure anaemia and some fever. Pulmonary tuberculosis is a much more common cause of moderate anaemia, especially in young adults, and now that facilities for chest radiography are available almost everywhere it should be recognized easily.

An important cause of simple chronic anaemia is nitrogen retention, chronic uraemia. If a patient has a very slowly progressing renal lesion he may have no complaints until his blood urea exceeds 100 mg. per 100 ml., and his haemoglobin has sunk to, say, 60%. In such cases the haemoglobin level and blood urea are reciprocally related, so that if the blood urea can be lowered the haemoglobin level will rise. Such patients usually have an acidosis secondary to the renal lesion, and if this is present, as shown by a diminished alkali reserve (plasma bicarbonate), then administration of alkali (sodium bicarbonate) in quantities sufficient to raise the alkali reserve to, and to maintain it at, the middle of the normal range (68 vols. per 100 ml. or 30 mEq per litre) will result in a reduction in the blood urea and an increase in haemoglobin level. By this means a patient with nitrogen retention due to polycystic kidneys may be kept alive and useful for several years after he would have died from uraemia had he not been treated. This may be of great importance to the family of such a man, in whom death usually occurs during the fifth decade, when his children still need him; it is equally important for the child or young adult with renal rickets, whose bony lesion may be healed by precisely the same procedure. It is always desirable to estimate the blood urea in a patient with unexplained simple chronic anaemia, and, if it is raised, examination of the urine for cells and casts, careful palpation of the abdomen for polycystic kidneys, adjustment of the alkali reserve to the optimal figure, and perhaps an excretion pyelogram may be reasonable procedures.

There are other unrelated conditions which diminish red-cell production: some simulate an infective process—for example, rheumatoid arthritis; others appear to be neoplastic, such as Hodgkin's disease and other reticuloses, but in these the anaemia is rarely the presenting symptom, as it is often in uraemia and sometimes in infection, rather is it a symptomatic epiphenomenon. Occasionally one encounters a simple chronic anaemia in an obese woman, usually slow witted, who feels the cold very severely, who snores or who speaks slowly with a nasal intonation, and whose hair and eyebrows are greying and scanty. In such patients one can but suspect myxoedema, and a raised serum cholesterol would support that diagnosis and warrant further investigation, including a B.M.R., though photographs before and after a month's course of thyroid extract offer more convincing diagnostic evidence than does the B.M.R. One form of myxoedema can be caused by absorption of resorcinol from ointments or suppositories containing it, usually in middle-aged women with varicose ulcers.

Drug-induced chronic anaemia or chronic anaemia resulting from poisoning are both rare. Benzene inhaled from rubber solutions, dry-cleaning fluids, paints and varnishes, motor spirit, or from solvents may cause a hypoplastic anaemia, with leucopenia and thrombocytopenia developing during exposure or months or years thereafter, but this is rare in Great Britain. A similar anaemia may develop after the administration of chloramphenicol, though little is known of its frequency. Lead-poisoning is usually accompanied by a moderate anaemia with punctate basophilia, but should not be diagnosed merely because the blood cells show excessive punctate basophilia; one cannot say that a patient has been poisoned unless he develops symptoms or suffers organic damage. Not rarely a subject absorbs and excretes some lead without developing any symptoms, and if on the discovery of punctate basophilia he is said to have lead-poisoning he may well develop a compensation neurosis and manufacture symptoms. If lead absorption or even poisoning is suspected from the blood count, one should not suggest that the patient is "suffering from lead-poisoning" but should suggest that, "since he has been exposed to lead, it would be wise to discover how much he has absorbed" and arrange for an analysis of a 24-hour specimen of urine. If he has wrist-drop or abdominal colic and his lead excretion is excessive one has no alternative but to make the diagnosis of poisoning.

Unusual Blood States

There remain a few conditions which should be regarded as physiological aberrations, or necessary consequences of disease. Chronic retention of carbon dioxide is found in emphysema, and is accompanied by an increase in mean cell diameter up to 8.8 μ without increase in variability—a change also seen occasionally in congestive cardiac failure.

Unexplained macrocytosis without anisocytosis and without anaemia is rare and may be ignored if haemolytic anaemia and carcinomatous deposits in the bone marrow can be excluded. In obstructive jaundice the red cells become excessively thin and target cells are common, even though there is no iron deficiency; rarely, obstructive jaundice can thin the cells of acholuric jaundice (congenital spherocytosis) so much that fragility becomes normal. Occasionally, ovalocytosis, in which the cells are ellipsoidal disks, may be seen and must be differentiated from pernicious anaemia; in ovalocytosis anaemia is slight or absent and anisocytosis minimal. If necessary, a sternal puncture would show megaloblastic erythropoiesis in pernicious anaemia and normoblastic erythropoiesis in ovalocytosis.

It may be noted that no anaemia has been ascribed to vitamin deficiency. In Britain to-day such anaemias are so rare that no haematologist would consider such a diagnosis without a clear history of dietary deficiency and the symptoms of scurvy, beriberi, or pellagra. On the other hand, dysphagia with stomatitis, the so-called "Plummer-Vinson syndrome," may occur in elderly women who are not anaemic, and is then due to riboflavine deficiency.

THE WILLIAM BUDD HEALTH CENTRE

THE FIRST YEAR

BY

R. H. PARRY, M.D., F.R.C.P., D.P.H.

J. SLUGLETT, M.B.

AND

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The William Budd Health Centre in Bristol, one of the first to be provided under the National Health Service Act, 1946, was opened officially on September 16, 1952, by the Minister of Health, Mr. Iain Macleod.

A full description of the buildings has been given elsewhere (*Lancet*, 1952), but a brief résumé may not be out of place here. It is a prefabricated single-story building of "Orlit" construction containing six general-practitioner suites, each with its own waiting-room, surgery, and examination-room; a main waiting-hall; a large office; a staff room; a medical treatment room; and the usual offices. The practitioners were not in group partnership, and the centre was to cover their branch practices. All rooms were to be used either by general practitioners or by the local health authority, but in general the former used the centre mornings and evenings, the latter in the afternoons. The centre was provided to serve a housing estate covering some 1¼ square miles, with a population of 30,000, on which there lived no medical practitioner, although the periphery of the estate was well served with general medical and dental practitioners, pharmacists, and two local authority clinics.

It is a matter of some importance that all those who are interested in the health services of this country should be kept informed of the progress made in the few experimental health centres which have been set up. This article contains the substance of the first annual report of the House Committee.

Throughout the past 12 months the centre has been visited by legislators, administrative, health, and social workers from all parts of the British Isles, Europe, the Americas, Scandinavia, and South-east Asia. Almost without exception the visitors' reports have been very favourable.

The period under review has been one of rapid evolution of the health services in the area served by the centre. It is now true to say that in no other district in Bristol, and possibly in the whole of the country, is there such close co-ordination of medical services or such excellent co-operation between the medical and ancillary staffs employed in the field by various health and welfare administrative bodies.

The original staffing arrangements to cover both practitioner and local authority work within the centre included a sister-in-charge, a deputy sister, and three nurses; two secretary-typists, one general clerk, two porters, and two part-time sisters. Experience has enabled us to effect some economy, and the staff has now been reduced by one nurse and one secretary-typist, although the doctors' evening surgeries necessitate the additional employment of part-time sessional clinic nurses. It should be noted that because of the special circumstances in the area full nursing cover for a day and night service had to be provided (*Lancet*, 1952). The nurses live in a near-by hostel.

Time-table

Although there was some apprehension at first that the accommodation at the centre might not be fully used for large parts of the day, Table I shows that, in fact, almost every room is in full use from 9 a.m. to 8 p.m., Monday to Friday, inclusive.

Adhering to the original plan, the practitioners use the suites in the mornings and evenings and the local authority in the afternoons. This arrangement has proved highly satisfactory, and the fact that the practitioners' surgery hours are staggered (this was purely chance and not planned) has helped to prevent congestion and overloading of staff, and has facilitated the cleaning of rooms. The rooms are prepared by the centre staff for the next user.

TABLE I.—*Surgery Hours*

Firm of Doctors	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			Morning			
D	9–10	9–10	9–10	9–10 (I.W. by appt. 10–10.30)	9–10	9–10
B	9.30–10	9.30–10	9.30–10	9.30–10	9.30–10	9.30–10
A	10.30–11 Dr. a	10.30–11 Dr. b	10.30–11 Dr. a	10.30–11	10.30–11 (I.W. by appt. 11.30–12)	10.30–11 Dr. a
F	11–11.30 Dr. c	11–11.30 Dr. d	11–11.30 Dr. c	11–11.30 Dr. d	11–11.30 Dr. c	11–11.30 Dr. d
E	11.15–12	11.15–12	11.15–12	11.15–12	11.15–12	11.15–12
C	12–12.30	12–12.30	No surgery	12–12.30	12–12.30	12–12.30
			Afternoon			
C	Inf. welfare 2.30–4.0		Wednesday Afternoon A.N. clinic by appt.			
A, D .. .. B, F						
D	5.0–5.45 Dr. e	5.0–5.45 Dr. e	5.0–5.45 Dr. e	5.0–5.45 Dr. e	5.0–5.45 Dr. f	No surgery
A	5.15–6.0 Dr. a	5.15–6.0 Dr. a	5.15–6.0 Dr. a	No surgery	5.15–6.0 Dr. g	No surgery
F	6.0–6.30 Dr. d	6.0–6.30 Dr. d	No surgery	6.0–6.30 Dr. c	6.0–6.30 Dr. d	No surgery
E	6.30–7.0	6.30–7.0	6.30–7.0	No surgery	6.30–7.0	6.30–7.0
B	7.0–7.30	7.0–7.30	No surgery	7.0–7.30	7.0–7.30	No surgery
Local authority clinics .. Session 1.30–4.30 p.m.	Mids., A.N.C., school med. sess.	Inf. welfare	Inf. welfare	Relaxation; mothercraft	A.N.C.C.	
			Nutritionist	Sch. med. sess.	A.N., P.N., B.C.C. clinic	

During the period under review 10 doctors attended the centre at some time or other, but the bulk of the work was done by one or other of the principal partners of the six firms mentioned. It should be noted that four of the doctors are now using the centre in the afternoons for the purpose of carrying out antenatal and infant welfare clinics for their own patients. School medical sessions in the charge of a medical officer engaged for the purpose by the local authority have been held on two afternoons a week since January, 1953. A consultant obstetrician session, a nutritionist's session, and relaxation and mothercraft sessions have also been in operation from an early stage.

General-practitioner Work

Statistics are appended of the volume of work undertaken in the centre from August, 1952, to July, 1953.

Patients Registered at the Centre.—Although there is a population of about 30,000 at risk, Table II shows that only just over 10,000 people on the lists of the general practitioners concerned attend there for examination or treatment.

TABLE II.—*Total Patients Registered at the Centre*

1952		1953						
Nov. 9,473	Dec. 9,565	Jan. 9,732	Feb. 9,850	Mar. 9,993	April 10,153	May 10,248	June 10,332	July 10,354

Between 20 and 30 practitioners other than the health centre doctors have patients on the estate, and these people, living mostly on the periphery, find it more convenient to attend these doctors or the main practice premises of the participating doctors, which are just outside the area. Two local authority clinics also serve the periphery of the health centre area. Moreover, before the centre came into operation a busy minor ailment school clinic was in operation within the grounds of one of the schools on the estate, and this has remained for continuation treatment. For these and other reasons it cannot be claimed that the health centre is, in fact, serving the main medical needs of 30,000 people.

Patients' Attendances at the Centre.—Table III shows the quarterly attendances of patients to each practitioner firm. On average, 8,261 patients attended each quarter; the busy winter quarters November to January and February to April are noteworthy.

TABLE III.—*Quarterly Attendances for Each General-practitioner Firm*

Firm of Doctors	1st (Aug.-Oct.)	2nd (Nov.-Jan.)	3rd (Feb.-Apr.)	4th (May-July)
A ..	2,735	3,419	3,734	2,699
B ..	135	412	472	365
C ..	340	591	488	402
D ..	1,477	2,054	2,348	1,717
E ..	1,092	1,271	1,450	1,109
F ..	989	1,222	1,419	1,105
Total..	6,768	8,969	9,911	7,397

An average of 8,261 patients were seen by G.P.s at the centre each quarter.

Practitioner Special Clinics.—Table IV relates to the recently started maternity and infant welfare clinics operated by the practitioners. This development is very promising, as the doctors see their expectant mothers in association with the district municipal midwives and health visitors; the hospital specialist obstetrician is also available for consultation if required. Thus the patient, instead of having to visit midwife, general practitioner, local authority doctor, and hospital specialists on separate occasions in different places, has only one place and visit, at which all her antenatal care is given, including mothercraft teaching and relaxation. Only one, instead of four, sets of notes is in existence for each patient. Similarly, the doctors conducting their own infant welfare clinics have the advantage of the co-operation of the health visitor in general health education and special teaching in infant care. A fuller description of this service will be given elsewhere.

TABLE IV.—*Attendances During 1953*

Firm of Doctors	At G.P.s' Antenatal and Post-natal Clinics	At G.P.s' Infant Welfare Clinics
A	205 (27 sessions)	310 (28 sessions)
B	79 (18 „)	—
C	—	296 (28 sessions)
D	239 (28 sessions)	112 (27 „)
F	106 (26 „)	—
Total ..	629	718

Work in the Medical Treatment Room.—Table V shows the number of "treatments" given by the nurses for each practitioner firm. The treatments include dressings, injections of penicillin, insulin, liver preparations, and so on. The number of "casuals" given treatment—that is, patients not on the health centre doctors' lists—is also given for each quarter. For the first few months the purpose of the centre was misunderstood; the population regarded it as a casualty out-patient department and used it, often for trivial complaints; a few outside practitioners thought they could refer their patients for treatment to the centre. By personal instruction and group talks to local organizations the purpose of the centre is now better understood. There has been a falling off in the number of casuals until the summer months, when the lighter evenings put local children at longer risk. However, no genuine emergency is turned away from the centre. Arrangements are made to call the appropriate doctor or to order an ambulance to send the patient to hospital, or initial treatment is given and the patient is referred with a note to his or her own doctor.

TABLE V.—*Treatments Given for Each General Practitioner (Quarterly)*

Firm of Doctors	1st (Aug.-Oct.)	2nd (Nov.-Jan.)	3rd (Feb.-Apr.)	4th (May-July)
A ..	980	1,334	1,236	948
B ..	21	80	54	59
C ..	180	201	153	79
D ..	666	767	542	380
E ..	211	126	57	49
F ..	465	469	344	308
Total..	2,523	2,977	2,386	1,823
Casuals..	120	48	63	98

The quarterly average of patients treated, apart from casuals, is 2,425.

Night Calls.—Table VI shows the night calls (8 p.m.–8 a.m.) dealt with at the health centre. Here we should explain that the estate residents asked in the planning stage that some form of night service should be made available. At one stage serious consideration was given to the provision of sleeping quarters for a practitioner within the centre. For various reasons this idea was rejected and night cover is now provided by having a porter on duty each night, during which he attends to night inquiries and also cleans the centre. The nursing staff, who live in the vicinity, work a night rota and are on call when needed by the porter. It should be noted that the doctors had estimated the need to cover between 10 and 12 calls a night. It will be seen from Table VI that, in fact, calls have averaged 1 to 2 a night, and in the light of this experience a doctor's flat would have been needless. How far the fewness of the night calls is the result of the psychological reassurance of an ever-open health centre it is difficult to say. Out of 543 "out of hours" calls a nurse had to be called on 150 occasions—that is, an average of 12.5 per month.

TABLE VI.—*Night Calls (All Types)*

Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apl.	May	June	July
19	36	34	30	47	52	35	47	52	51	69	71

Average per month, 45+.

Use of and Reference to Specialist Services.—(1) The centre consultant antenatal clinic:—From an early stage an obstetric specialist from the professorial unit has held a

regular consultant session at the centre. His services have been freely available to general practitioners and to the local authority doctor and midwives; personal contact with him has been most valuable. Twenty-four sessions have been held, at which 374 patients were seen, an average of 15 per session. (2) Reference of patients to hospital and specialist services:—Table VII shows the number of patients referred

TABLE VII.—*Patients Referred to Hospital Diagnostic Units (All Doctors and Local Authority)*

	Routine Chest X-ray Exams.	Haemoglobin	Complete Blood Count	Microscopical Exam. of Urine
Total .. (Jan.-Sept.)	328	356	79	63

to hospital diagnostic units by practitioners and local authority doctors for some of the more important special investigations. Table VIII shows the number of patients referred to hospital consultants by general practitioners. It should be noted that in accordance with the practice in

TABLE VIII.—*Patients Referred to Hospital Consultants (All Doctors)*

	Orthopaedic	Paediatric	Physicians	Surgeons	E.N.T.
Total .. (Jan.-Sept.)	55	41	253	224	45

all Bristol local health authority clinics every expectant mother is encouraged to have a routine chest *x*-ray examination, which is provided by the local authority at the central clinic; this practice is being followed at the William Budd Health Centre.

Local Authority Work

Antenatal Clinics.—The medical officers hold one session a week at the centre in order to give antenatal care to expectant mothers living in the area whose doctors do not work in the centre. At 24 sessions there have been 403 attendances—an average of 17 patients a session. The district midwives hold two sessions a week, and at 26 sessions have had 371 attendances—an average of 14 a session.

Infant Welfare Clinics.—At 44 sessions 1,992 children were examined or advice was given to the mother:

Under 1 year old ..	1,237,	average 28	a session
1 year old	384	9	„ „
2–5 years old	371	8	„ „

Pre-school children on the lists of the health centre doctors are now not seen by the local authority doctor, although the latter's past knowledge and records of the child are useful to the health centre doctors.

School Medical Clinics.—There are two school medical officer's sessions a week. At 57 sessions there have been 1,215 attendances, an average of more than 21 a session. Schoolchildren on the lists of the health centre doctors do not attend these clinics.

Physiotherapy: Antenatal and Post-natal Exercises (Relaxation Classes).—At 21 sessions 105 patients attended—an average of 5 a session. This includes both local authority doctors' patients and those of the health centre doctors.

Nutritionist's Clinic.—The local authority nutritionist attends the centre for one session a week, in order to give dietetic advice to general-practitioner patients. The "gastric ulcer," "diabetic," "reducing," etc., diets prescribed by the doctors have been translated into practical daily diets worked out in accordance with the patient's financial means. There were 127 attendances.

Repercussions on General Practice in the Area

New Patients at the Health Centre.—By agreement, any new patient expressing preference is put on the list of the doctor of his choice. Unattached new patients attending the centre and with no special preference for any one doctor have been allocated to each doctor in rotation. The number of such new patients on each doctor's list has been reviewed each quarter so as to keep a fair allocation.

Transfer of Patients in the Area ("Drift").—The additions to and deletions from the lists of all doctors working at the centre (including their partners, if any) for the first year were:

Total counts of the lists of the doctors concerned on July 1, 1952	29,206
Additions during the year	3,460
	32,666
Deletions during the year	2,840
Total counts on July 1, 1953	29,826
Net increase	620

It is probable from these figures that there has been no abnormal drift to or from the lists of the doctors connected with the centre during the year.

Co-operation of Health Workers.—One of the most important and significant developments in this area has been the tremendous improvement in co-operation between the general practitioner and the local authority health and welfare workers in the area. Mention has already been made of the greatly improved co-ordination of maternity services in the area and of the developing interest of the general medical practitioners in orthodox preventive medicine, as evidenced by their starting infant welfare clinics for their own patients as part of their general medical service. Further extension along these lines would lead to the exclusion of the local authority doctors without any loss in the efficiency of the preventive health services. In addition, there is now excellent co-operation between the three district health visitors based on the centre and the practitioners. The doctors appreciate that the health visitor can be as valuable to them as the midwife and district nurse, and many misunderstandings on both sides have been removed.

Standard of General Practice in the Area.—It is difficult to assess the standard of any general practice, and it would be invidious in this report to make extravagant claims about general practice at the William Budd Health Centre. However, the secretarial and nursing assistance has given the doctors more time to examine and advise their patients. The treatment room, in which an increasing volume of work has been undertaken, has enabled many patients to be treated who would otherwise have gone to hospital out-patient departments.

Agreements.—The official machinery set up to deal with the health centre is as follows: (1) The Joint Advisory Committee with no executive functions. On it sit members of the local health authority, the executive council, the local medical committee, and the house committee. It gives advice on policy matters to the two parent bodies—the local health authority and the executive council—and was set up to ensure fair representation of the views of each authority and of the health centre workers as well as the doctors who work in the area but not in the centre itself. (2) The House Committee, consisting of the health centre doctors, the representative of the medical officer of health, the sister-in-charge, and the secretary of the executive council. It deals with domestic matters. The Joint Advisory Committee has met on five occasions—three of them before the centre was opened—and the House Committee on five occasions. No formal agreements have been in force either between the executive council and the local health authority, or between the council and the doctors, or between the doctors themselves. At an early stage the question of rent was informally agreed by all concerned, and as the centre has evolved the various parties have honoured the decisions of the two committees.

Finance

The gross cost of operating the centre for both local authority and practitioner services is within £65 of the estimate made two years ago—namely, £10,000 per annum, or £200 a week. This covers loan charges, salaries, uniforms and laundry, local authority drugs and dressings, equipment, upkeep of nurses' hostel, maintenance and repairs, rent,

rates, heating, lighting, water, printing and stationery, telephone, but does not include capitation fees, the proportion of the salary of the local authority doctor, the regional board specialist, and the cost of the drugs prescribed.

Discussion

No doubt it would be interesting to discuss the first year's experience at the William Budd Health Centre in the light of the Hadfield Report (1953), the Review of General Practice by the General Practice Review Committee of the B.M.A. (*British Medical Journal*, 1953) and the articles by Joseph Collings (1953) on group practice. Space does not permit this, but we would point out that all these reports, in their references to health centres, are discussing a theoretical conception, as none of those authorities have had the opportunity of first-hand experience of the functioning of a health centre under the National Health Service Act. We must limit our discussion to our own experience and try to give answers, albeit provisional, to some of the questions that have been asked.

Let us say at the outset that, so far, the health centre has provided many advantages to the patients, doctors, and other health workers in the area, and few if any disadvantages that we have been able to discover.

The two most promising developments are the relief of the doctors from "unproductive" work by the provision of clerical and nursing assistance, thereby enabling them to devote more care and attention to their patients, and the greatly improved co-ordination of health services and co-operation of health workers in this area.

The theoretical conception that co-operation and co-ordination would be improved by allowing health workers of all types—general practitioners, local authority doctors, district midwives, and health visitors—to work under one roof has been borne out in practice. Reference has already been made to the closely knit maternity services in this centre with the attendant advantages to all concerned, and not least to the expectant mother. The staff room has proved to be the most important room in the building, for it is there that all medical, nursing, and social workers in the district (including probation officers, children's officers, voluntary case workers, and the like) forgather and meet the doctors to discuss particular patients or their families over a cup of tea or coffee. With greater rapidity than had been expected, the health and social workers in this area are welding themselves into a team which has the interest of the patient and family at heart, and each member of the team is now in the favourable position of being fully informed on all known factors operating in each case.

Nevertheless we would not say that such a happy development would necessarily follow in every health centre. Two main factors have helped at the William Budd Health Centre. The relatively small size of the centre, together with the joint use of rooms by general practitioners and local authority staff, instead of resulting in disagreements as might theoretically be expected, has resulted in closer co-operation. Secondly, we feel that our early decision that a nursing sister should be in overall charge of the centre rather than a lay manager was the right one. Much has depended on her in achieving co-operation; her qualifications and experience enable her to smooth out day-to-day difficulties in a manner which could never have been achieved by even the most charming of lay administrative officers.

The original objective in this health centre was to provide suitable premises for general practitioners, and in the planning stage the local authority services were of secondary importance. As time has gone on we have found the need for, and proved the advantage of, other services. For example, the specialist obstetrician has been brought in, relaxation classes for expectant mothers have been started, and the advice of the local authority nutritionist has been made available to the doctors. This nutritionist's clinic is proving a unique and valuable undertaking and will be reported on more fully at a later date. The general practitioners are unanimous in their belief that the provision of *x*-ray and minor pathological investigational facilities would be a great advantage to the patients and to themselves, and this is the direction in which they would like to see future developments.

One of the frequently expressed fears about health centres was that there would be local authority interference and dictation in their management. Such fears have proved groundless. Apart from the good will displayed by all concerned, we think the machinery set up, which includes a house committee and a joint advisory committee, has done much to facilitate the smooth running of the centre.

Fears were also expressed that health centre practice would be too remote and impersonal and would interfere with the doctor–patient relationship. This has not happened at the William Budd Centre. We believe that the provision of a separate waiting-room for each doctor's suite has helped to preserve the doctor–patient relationship. But the attitude of the secretarial and nursing staff is just as important. In this we have been fortunate. Most of the patients attending are now well known to the staff not merely as human beings but as human beings who are being attended by Dr. A, B, or C as the case may be.

It is difficult to canvass the opinion of patients attending the centre, but none have complained of an impersonal service or have deliberately transferred to a non-health-centre doctor. The patients have an undoubted sense of security in that they know the health centre is always open and they can always get service if they need it.

It should be noted that so far there has been no move towards a group practice in the sense of financial partnership. In other ways, however, the relationships of the doctors have become a good deal closer; for example, seeing and treating emergency patients on behalf of each other is now customary and relief in other ways is developing. Collings (1953, p. 611), the great advocate of group practice, has written: "The aims of basic group practice are identical with those of ordinary general practice. The primary aim is to provide patients with the highest level of diagnostic and therapeutic service attainable outside hospital, to inconvenience the patients as little as possible, and to preserve the best elements of personal service—all at a cost the patient (or better, the community or nation) can afford."

We think this is being achieved at the William Budd Health Centre without formal financial partnership but with the advantage that each practitioner firm maintains its individuality and that the patient can indeed be sure that he will see the doctor of his choice and not any one of half a dozen or more different members of a group practice.

Collings was careful to qualify these aims by reference to what the nation or community can afford, and here we should like to comment on the financial aspects of this health centre. It is true that it is costing £10,000 a year, but this is for fairly extensive local health and education authority services for 30,000, together with general medical services for some 10,000 people. This is a lot of money, but let us keep a sense of proportion. Even if the general medical practitioners had not participated in this project there would have been a need for, and statutory duty to provide, local authority services. The capital cost for the building would have been about the same and the maintenance may have been halved, but the centre would have been lying idle for many sessions a week. Indeed, there must be many hundreds of good local authority clinics which could be used with advantage by general medical practitioners without necessarily curtailing the local authority services. The sooner arrangements of this kind can be made the sooner many local authority doctors will relinquish their "clinical duties" in maternity and child welfare and minor ailment clinics. Moreover, the practitioners, relieved of non-productive work, can then turn their attention to the preventive and promotive aspects of health work. One other word on finance—and we say

this in no carping spirit—the cost of all the principal activities in the centre is no greater than buying part of the services of two consultants in receipt of a special merit award.

It is already apparent that many patients have been treated who, but for the health centre, would have gone to hospital out-patient departments. With further aids, such as a small laboratory and the help of a laboratory technician and facilities for simple radiography, there can be little doubt that not only will the patients benefit but the practitioners' interest and standard in general practice will be further stimulated and, not least important, the overworked hospital out-patient department must be still further relieved.

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Nova et Vetera

RICHARD MEAD: PIONEER AND PATRON

Before Barry built the vast brick and terracotta Hospital for Sick Children at Great Ormond Street, there existed at the corner of Powis Place a fine old Queen Anne mansion where for the last twenty-four years of his life Dr. Richard Mead lived, as Dr. Johnson said, "more in the sunshine of life than any other man." He was pre-eminently great in an age of great practitioners—the epitome of accomplishment in the fullest meaning of that word. For Mead enjoyed the best of both worlds, basking, like Sloane, in the approval accorded to generous patrons, and esteemed, like Cheselden, as a reliable physician. Pope has caught both qualities with his lines:

> And Books for *Mead*, and Butterflies for *Sloane*

and

> I'll do what Mead and Cheselden advise,
> To help those limbs and to preserve those eyes.

His life illustrates the rich leaven which Nonconformity brought to English scientific and medical thought in the seventeenth and eighteenth centuries. Born at Stepney in 1673, he was first educated at home by his father, an eminent Nonconformist divine, then by two successive tutors until, at the age of 16, since Oxford and Cambridge were barred to him by the Test Acts, he proceeded to Utrecht, where he studied classics and philosophy for three years. He spent a further three years at Leyden, where he worked alongside Boerhaave, and then, with his brother and two others, he toured Italy, taking his doctor's degree in philosophy and physic at Padua at the age of 22.

At Stepney, too, began his professional career, where his father assisted, even to the extent of recommending him from the pulpit. His first published work showed that he had assimilated the teaching of Archibald Pitcairne at Leyden. Entitled *A Mechanical Account of Poisons* (1702), it accounted for the effects of several poisons by their admixture with the blood. An abstract of this, published in the *Philosophical Transactions* of the Royal Society for 1703, not only secured his election to that body but appointment as physician to St. Thomas's Hospital in the same year.

Moving as he did in wider circles, he took up residence in Crutched, and later in Austin Friars, adding further appointments *en route*—the readership in anatomy to the Company of Barber Surgeons, the vice-presidency of the Royal Society, and the doctorate of medicine of the University of Oxford. This last honour enabled him to be admitted to fellowship of the Royal College of Physicians, of which he subsequently became a Censor, Harveian Orator, and lived to refuse the presidency.

"Mead, I love you," said the irascible but generous John Radcliffe, "and I'll tell you a secret to make you a fortune—use all mankind ill." Though Mead took over Radcliffe's house and practice in Bloomsbury Square in 1714, he did not take his advice. On the contrary. When Watteau, the distinguished painter, came especially from the Continent to secure his help in arresting his consumption, Mead commissioned him to paint two pictures, and this generous patronage was extended to a variety of others. He secured the liberation of Dr. Freind from the Tower of London, where he was imprisoned, and pardon for the Reverend G. Kelly. He was without a rival as a practitioner, making an average of from £6,000 to £7,000 a year. He attended the King, the Prime Minister, Sir Isaac Newton, and Bishop Burnet among others. A pioneer in public health, his *Short discourse concerning Pestilential Contagion and Methods to be used to prevent it* was first published in 1720 and ran to seven editions in twelve months and more afterwards. In it he recommends, as a first step, the establishment of a Central Council of Health, armed "with such powers as might enable them to see all their orders executed with impartial justice." He urged that the sick should be isolated in "clean and airy habitations" sustained at public expense.

After 1720, when Mead removed to Great Ormond Street, he built a large gallery at the bottom of his garden to house his treasures. Here he would entertain Richard Bentley, the formidable Master of Trinity College, Cambridge (over whom he possessed great influence), and Martin Foulkes, the antiquary. It was here, too, on February 16, 1754, that Richard Mead died, surrounded by over 10,000 books and numerous *objets d'art*. Unlike his great contemporary and friend, Sir Hans Sloane, no steps were taken to acquire his collection, and it was dispersed by auction. Sir Hans Sloane's name lives on both at Chelsea and at the British Museum, John Radcliffe's by the museum and observatory which bear his name at Oxford, but Mead's links with the present are more tenuous if equally binding. For it was he who persuaded the bookseller Thomas Guy to erect a new hospital at a cost of £18,793, increased by an endowment of £200,000 on Guy's death in 1724.

W. H. G. ARMYTAGE.

Preparations and Appliances

A REST CHAIR FOR ARTHRITICS

Dr. H. F. WEST, physician-in-charge, Sheffield Centre for Investigation and Treatment of Rheumatic Diseases, writes: Patients with painful and stiff hips or knees usually find great difficulty in getting in and out of ordinary rest chairs.

Being dependent on others in this matter they often spend too long at rest, stiffening up, or on their feet, developing oedema of the legs. The chair illustrated has been designed for such patients and is made in varying heights. A patient should have the highest chair he can manage to swing himself on and off. These chairs were made by Messrs. Shortall Ltd., Maltravers Street, Sheffield.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Intra-arterial Transfusion

SIR,—Substantial claims have recently been made concerning the life-saving properties of blood transfusion into an artery, and many cases have been reported in which this form of treatment has apparently been instrumental in saving a patient's life. It is difficult to assess from the available evidence how successful intravenous transfusion would have been in these cases, and there must be many who believe that the latter procedure will always be adequate, provided the vein is large enough and not in spasm and adequate pressure is available. There must also be many obstetricians who, in common with myself, have served on an emergency obstetric service ("flying squad") and have seen patients recover with intravenous transfusion following the most calamitous haemorrhage. I am recording the following case because prior to that experience I had believed that arterial transfusion was seldom, if ever, required and I have now changed my mind.

An apparently fit woman aged 35, with two children, delivered her third face to pubes after an exhausting second stage. There was an inert uterus and the placenta was expressed by her own doctor, who called for the "flying squad" after a loss of 40 oz. (1.1 l.). On my arrival the patient, who had continued to bleed, was in poor condition but apparently no worse than many others whom the service had treated successfully. Four pints (2.3 l.) of blood were given into the junction of the right saphenous and femoral veins, but there was steady deterioration of the patient, who continued to bleed slowly, and death occurred while the last pint (0.6 l.) was being run in. Necropsy showed that death had been due to heart failure and there was gross distension of the vena cava and great veins with the blood that had been transfused and which had not been passed on by the failing heart. It appeared that the continued loss had been due to a direct flow from the external iliac vein into the hypogastric and uterine veins on the right side.

There was nothing to suggest that this patient had any myocardial deficiency prior to her pregnancy, and there was no toxaemia. Her cardiac failure was presumably due to inadequate coronary blood flow following severe exertion and considerable haemorrhage. I felt in retrospect that an arterial transfusion might have delivered enough blood to the coronary vessels to save the failing heart, which was being embarrassed still further by the intravenous transfusion. I shall be interested to hear whether similar cases have arisen in the practice of other obstetricians.—I am, etc.,

Birmingham. W. G. MILLS.

Intra-arterial Thiopentone Injection

SIR,—Dr. M. Swerdlow's medical memorandum (*Journal*, January 30, p. 258) prompts me to describe a case which I encountered three weeks ago. The patient, a man aged 40, was having bouginage for stricture. It was intended to give about 0.7 g. thiopentone, followed by nitrous oxide/oxygen with a little trichlorethylene if needed. The patient's right forearm was covered with a network of very prominent veins, and injection was made into the median cephalic vein. After 0.5 g. of thiopentone had been injected, there was a slight leak, and the needle was withdrawn. It was intended to complete the injection into the median basilic vein, which appeared, as it often does, to consist of two parallel channels, both prominent under the skin. The needle was inserted into the more lateral of the two vessels, approximately at the spot marked X in the photograph in Dr. Swerdlow's article. Only 1 ml. had been injected here when the patient (by this time asleep) responded with a violent spasm of the flexor muscles of the arm; the medial side of the forearm and hand quickly blanched. The pulsation from this artery, which was a subcutaneous aberrant ulnar, was not transmitted to the syringe, which was immediately disconnected from the needle. Blood came from the hub of the needle in spurts. A syringe containing 5 ml. 1% procaine was immediately connected to the needle and its contents injected. By this time the blanching had passed off, and been replaced by mottling, which soon gave way to normal colour. Pulsation in the limb was normal then and subsequently, and the aberrant vessel could easily be felt pulsating under the skin, and on close inspection could even be seen to pulsate. The operation and anaesthetic were completed without further incident, and there were no untoward signs or symptoms in the arm thereafter. The patient stated subsequently that he had been anaesthetized twice before, but in each case the injection was made into his left arm. His attention was drawn to his abnormality, which was present in one arm only, and it was simply explained to him. He was told that he should draw the attention of anyone about to make an injection in his right arm to the pulsation in this vessel.

Accidents like this can only be avoided by palpating *every* vessel before injecting thiopentone into it, no matter how like a vein it may look.—I am, etc.,

Manchester, 21. T. D. CULBERT.

Renal Complications after Using Sulpenin

SIR,—We were interested to read Mr. J. G. Callanan's account of renal complications developing in a patient during treatment with "sulpenin" (*Journal*, January 16, p. 138). We have had a similar experience with this preparation in a child, and believe that the following brief account may be of interest.

A girl of 5 developed a respiratory infection. From the fourth day of her illness and for two days before admission to hospital she had been treated with "sulpenin." She had been given four tablets initially, followed by two tablets every four hours (total dose 20 tablets and 10 g. sulphonamide). On the morning of admission her urine was noticed to be blood-stained, and shortly afterwards she passed several large clots of blood unaccompanied by urine. On examination in hospital she was complaining of central abdominal pain although there was no tenderness in this region or in the renal areas. She had signs of mild bronchitis. Blood pressure was normal. The urine was heavily blood-stained and sulphonamide crystals were seen microscopically. The urinary output was adequate and the blood urea normal. She was treated with a high fluid intake and alkalis. The next day she was better and the urine contained less blood. She was discharged home after eight days, when laboratory examination of the urine was normal.

Fortunately anuria was not a feature in our patient and she recovered rapidly. Mr. Callanan thought that the sulphadiazine fraction of "sulpenin" was responsible in his case, but we have seen similar cases of renal complications caused by sulphamerazine, and many other cases are recorded in the literature (e.g., Dr. E. C. Atkinson, *Journal*, September 15, 1951, p. 674, and subsequent correspondence). We therefore felt more inclined to implicate the latter drug, but the matter is debatable and obviously "sulpenin" is a preparation to be used with caution.—We are, etc.,

T. COLVER.
Sheffield, 10. J. C. HAWORTH.

Methylpentynol

SIR,—I was interested in your annotation (*Journal*, August 22, 1953, p. 435) on the use of methylpentynol as an alternative to the barbiturate hypnotics. I have tried it on a number of patients in hospital for this purpose, but without notable success. Those who were used to the barbiturates found it ineffective in doses up to 1 g., and, though it sometimes secured sleep rapidly in new patients who were anxious, they were usually awakened several hours later by the customary nocturnal noises of a hospital ward. I have not used it for patients in their own homes, where it might well be effective for insomnia associated with anxiety.

I would, however, like to draw attention to its use for premedication. I have used it successfully in a number of cases

before ward procedures such as paracenteses, biopsies, and lumbar punctures. The patient was given 500 mg. of methylpentynol (two capsules of "oblivon") about 10 minutes before the procedure began. In no case was anxiety marked, though in several of the patients similar procedures, previously performed, had been associated with considerable apprehension. In an endeavour to reduce the suggestion factor, some patients were not told the purpose of the drug; in those cases the drug seemed no less effective. In one case where anxiety was severe, 10 minutes after giving 500 mg. of methylpentynol it was possible to proceed with a patient in a state of calm co-operation. In no instance were there any complaints of side-effects or after-effects, and I observed none. No patient went to sleep as a result of administering the drug, nor was there any complaint of drowsiness at the time.

I have not attempted a controlled therapeutic trial, and I am well aware that it is easy to persuade oneself that an anticipated reaction to a drug has in fact occurred. I believe that methylpentynol is being used in dental practice, which should provide opportunities for just such a trial, and I shall be interested to hear what impressions are gained in this field.—I am, etc.,

London, N.19. A. G. BOAG.

Piperazine in the Treatment of Threadworms

SIR,—The article by Dr. R. H. R. White and Mr. O. D. Standen (*Journal*, October 3, 1953, p. 755), in which piperazine is recommended for the treatment of threadworms as being a harmless drug without side-effects, has surprised me. The authors have added in their letter (*Journal*, December 5, 1953, p. 1272) that in giving piperazine the weight of the patient should be taken into account in measuring the dose, but this seems to me insufficient, because piperazine is a drug which can paralyse the respiratory centre. I once gave piperazine by mouth to rats and I found it quite toxic. At 4 to 5 g. per kg. there was laboured breathing and twitchings, and some of the animals died. If not enough attention is drawn to the toxicity of this drug there is a risk that mothers, if there is no therapeutic effect, will increase the dose or repeat it at short intervals.

The reason for my letter is to call attention to the danger of this preparation and to recommend that it should be given only under direct medical supervision and not to out-patients.—I am, etc.,

Berne. T. GORDONOFF.

Inquiry about Anaesthetics

SIR,—At one hospital in which I work, and presumably in other hospitals, a few duplicated foolscap forms have been received under the heading "Ministry of Health. Anaesthetics in Hospitals. January 21 (9 a.m.)—28 (9 a.m.)." In the brief instructions which follow it is stated that details should be inserted on the opposite side of the form of every anaesthetic given during the above week. After explaining how this is to be done on the opposite side of the form, the instructions continue, "If during the week a death has occurred which has been thought to be due to an anaesthetic, information about this case should be given; also details should be supplied of any fire or explosion which has occurred in an operating theatre during the same week. . . ."

The forms in question were not sent to any of the doctors who might be concerned in the giving of anaesthetics, they are not marked "Confidential," and it has apparently been left to the group and hospital officials to see that the forms are completed.

I have written to the Ministry of Health asking for further information about this matter, but it may not be out of place to suggest that the publication of this letter would enable others to comment on this method of inquiry. Quite apart from the many other implications of this form, it does seem most improper that information is asked for about deaths which may be due to anaesthesia. Surely there are already properly established and legal methods of investigating such cases, and no hospital or individual should be asked to disclose details to the Ministry.—I am, etc.,

Radlett. R. S. MURLEY.

A New Oral Diuretic

SIR,—May I be permitted to comment on your annotator's remarks (*Journal*, January 16, p. 144) on "a new oral diuretic"? His assumption that general practitioners fight shy of administering medicaments parenterally is mistaken. In fact, they are given freely and for as long as they are indicated, provided they are of proven value. In our own practice, as in other practices, patients with congestive heart failure and other conditions requiring diuretic therapy, are given mersalyl regularly. Indeed, two of our patients have had mersalyl weekly for 15 years, with only occasional interruptions.

Your annotator's argument in favour of "mercloran" is surely self-destructive. Does he expect a general practitioner to submit his patient to a treatment which in two-thirds of the cases can produce such violent symptoms as "abdominal cramps, nausea, vomiting, diarrhoea, and bloody stools," and in the remaining one-third, to be discovered "by trial and error," the effectiveness of the oral diuretic is only one-quarter of the standard dose of mersalyl?—I am, etc.,

London, E.17. MYER COHEN.

Atomic Weapons and the Medical Profession

SIR,—President Eisenhower's recent appeal and the Russian reply have again raised hopes of the control or abolition of atomic weapons. Such a hope must be universal, and the need for agreement has been recognized by the Governments of all the big powers. Yet stockpiling increases, and on January 1 the *Daily Telegraph* stated: "One of the achievements (*sic*) of the New Year is expected to be the explosion of the first true hydrogen bomb."

The medical profession would be outstandingly involved in the event of an atomic war. Is there anything that we can do to help in the present situation? Here is one suggestion: The leaders of the profession could send an independent statement to their respective Governments stating the disastrous effects, in any country, of a hydrogen bomb attack upon the medical services (to which Governments and people alike look for aid in an emergency). This of course must be known to the Governments concerned, but the bald statement from a non-political source would serve to underline the urgency for agreement, and the document might just possibly strengthen their hands in discussion. Are there any other suggestions?

As stated in my previous letter (*Journal*, March 11, 1950, p. 610), any help, however small, that we can give would surely be preventive medicine of the greatest prophylactic value.—I am, etc.,

Hove. W. V. CRUDEN.

Variation in Human Milk

SIR,—I do not think that the conclusions reached in your leading article on "Variation in Human Milk" (*Journal*, January 30, p. 264) should pass without comment. You say that "if an infant is not gaining satisfactorily the explanation should be sought promptly. First, the possibility of infection or of constitutional disturbance should be considered. Either of these is, in general, more likely to be responsible than faulty or insufficient maternal milk. But if no such evidence is found additions to the diet in the form of complementary feeds should be given."

Surely before complementary feeds are given to babies with a weight gain which is not seriously defective the correct procedure is to try to increase the amount of breast milk which the baby takes—by giving him more frequent feeds if they are rather infrequent, by giving him longer on the breast if he needs it, by trying to ensure that the mother has more rest, and by stimulating her breasts to produce more milk by emptying them fully by manual expression after every

feed, giving the baby milk which has been expressed. Your advice, if taken, would cause a very large number of babies to be put quite unnecessarily on to the bottle.—I am, etc.,

Sheffield, 10. R. S. ILLINGWORTH.

The Unsaturated Fatty Acids

SIR,—I was very interested to read Dr. John H. S. Pettit's article (*Journal*, January 9, p. 79). During the past 12 months I have used on a number of eczematous patients, infants and adults, (*a*) the ointment alone, and (*b*) the ointment in conjunction with the capsules. No outstanding results were obtained, although some cases did respond to one dressing and one capsule daily, the treatment being carried out as well as possible in home surroundings.

From a general practitioner's point of view I agree that this treatment is in no way preferable to the already established ones—in fact, I have obtained quicker and better results from ointments containing coal tar, zinc oxide, etc. However, using the unsaturated fatty acids in cases of gravitational ulcer (predisposing causes established), I have had some very interesting results, mostly favourable—for example, a patient who has had a large and infected ulcer, resistant to all types of treatment for years, has responded well, the lesion now being almost healed. In this particular case one capsule is being taken and the dressing applied twice daily.

It would be very interesting to know if any of my colleagues have had similar results.—I am, etc.,

Leicester. ERIC LODGE.

The Feeble-minded

SIR,—There are two points arising from the correspondence which followed the publication of our survey of 12 mental deficiency institutions (*Journal*, January 2, p. 16) on which we should like to comment.

It has been suggested by Dr. G. McCoull (*Journal*, January 23, p. 214) that mental deficiency institutions in the London area may not be typical of those in the country as a whole. Fortunately we were able in April of last year to obtain material bearing on this point from Dr. W. Rees Thomas, Senior Medical Commissioner of the Board of Control, and with his permission this is given below. At that time the latest, and, in fact, the only, information possessed by the Board of Control with regard to division of patients by grade was that concerning long-stay patients for the year 1949 (i.e., those who were in institutions vested in the Ministry of Health on January 1, 1949, and who were remaining in them on December 31 of that year). These represented approximately 93% of all patients on the books of those hospitals in December, 1949.

The classification upon which the Board of Control figures are based is the sevenfold one contained in the International Statistical Classification of Diseases, Injuries and Causes of Death (1948). The categories are as follows: idiocy, imbecility, moron, borderline intelligence, mongolism, other and unspecified types, all other diagnoses. This classification is a mixed one, being based partly on the grade of the patient—idiocy, imbecility, and feeble-mindedness (or moronity), partly on clinical type (mongolism), and partly on extraneous and what sometimes appear to be irrelevant considerations.

Dr. Rees Thomas writes of the data: "In the category 'Mongolism' we have no information beyond the diagnosis given. The category 'Other and Unspecified Types' is equally unsatisfactory; of the 219 cases (20 male, 22 female age 0–15) 216 are returned as mental deficiency N.O.S. (not otherwise specified). The heading 'All other Diagnoses' (1,408 patients including 152 male and 120 female age 0–15) has 41 separate categories, none of which relate to grading. Examples are: head injuries, convulsions, encephalitis, epilepsy, asocial personality, and cerebral spastic infantile paralysis. In none of these cases can we find any information which will permit us to give you a grading." The categories "Other and Unspecified Types" and "All other Diagnoses" make up 3% of the total count. Dr. Rees Thomas also points out that the count of heads was made when the new G.R.O. cards were introduced, primarily to deal with admissions from January 1, 1949. The diagnoses "may or may not have a high degree of accuracy."

The most useful comparison between our London survey data and the Board of Control census figures is probably that between the proportions of adults in each of the three main categories by grade. This is given in the table below. Here mongols have been included among the imbeciles and the categories "other and unspecified types" and "all other diagnoses" have been grouped together under a separate heading.

Percentage of Adult Patients by Grade as Obtained in London Survey, 1951–2, and by Board of Control Census of Long-stay Patients

Grade	Board of Control Census		% of Patients by Grade Found in London Survey
	No. of Cases	% of Patients by Grade	
Idiot	1,721	4	3
Imbecile	14,809	33	39
Feeble-minded	27,122	60	58
Other	1,313	3	
Total ..	44,965	100	100

Allowing for sampling errors and difference in the manner in which the data were collected, the agreement between the two sets of figures is as close as could be expected. It thus seems very likely that the London data are comparable with what is to be found elsewhere in the country as far as grade of patient is concerned.

We do not wish to take up here in any detail the question of intelligence quotients. We would point out, however, that we did not claim that half the *total* number of defectives of all grades and ages had I.Q.s above 70 points on the matrices test, but merely that it seemed likely that the average intelligence quotient of adult feeble-minded defectives—that is, excluding idiots and imbeciles—aged between 16 and 29 years of age was above 70 points. The data obtained in the survey merely confirmed findings obtained by ourselves and others who have tested larger samples at individual hospitals on both the matrices and other intelligence tests.[1 2]

What is important, however, is not the average I.Q. of patients in mental deficiency institutions, but that three-fifths of the adult patients are "feeble-minded." Few will disagree that the feeble-minded present radically different problems in management from imbeciles and idiots.—We are, etc.,

N. O'CONNOR.
J. TIZARD.

London, S.E.5.

REFERENCES

1 Tizard, J. (1950). *J. ment. Sci.*, **96**, 889.
2 —— and O'Connor, N. (1952). *Lancet*, **2**, 620.

SIR,—Although I am sure that Drs. N. O'Connor and J. Tizard intended "A Survey of Patients in Twelve Mental Deficiency Institutions" (*Journal*, January 2, p. 16) to be unbiased, its presentation immediately gave rise to false conclusions and implications in the press (the *Star*, leader, January 4). I think that your own annotation (p. 35), Sir, was also not blameless. The general behaviour of mental defectives in hospital is quite good, but this is no criterion of social competency. The average intelligence quotient of young adult feeble-minded patients is 70 or more as stated, but I.Q., as we all know, is no index of social adjustment. Is the implication that we are not to have these people in mental deficiency hospitals at all, or that we do not supply suitable treatment to bring about social adjustment? Eighteen per cent. of our admissions last year were Section 8 or 9 cases. I consider that if these patients find a regime here, orientated towards social rehabilitation (as they do), they benefit far more by our efforts than by other treatment or punishments available.

To quote Section 8 and 9 cases as the problem groups is quite false. All feeble-minded people present some social problem, either of inadequacy or aggression, and a patient admitted under Section 6 for prostitution and incestuous behaviour in a family where all the members have visited prison, approved or special schools is, although polite and well-behaved here, a graver social problem than many a slight case of larceny. To say that half of our patients need no special nursing or supervision depends on how you look at it. One might as well say that all the boys in

a boarding-school need no special care or supervision. You cannot put untrained people in general charge of high-grade patients, and the good trained nurse who lives with them is worth his weight in gold. Epileptic patients may have no fits, or very rare attacks, but the case papers must show them to be epileptic. Otherwise we will be sending them out to risk falling off scaffolding or into machinery. Whether they are on or off the "live" list in the hospital is a different matter. The bald statement in the survey implies that they are detained in the hospital *only* because they are epileptic. The term "wages," even in inverted commas, is most unfortunate, and to include 73 children, 15 idiots, and an unspecified number of low grade imbeciles in a "wages" group is inadmissible. The group of patients in outside employment receives adequate spending money in any well-run hospital and many other perquisites besides. The long-stay cases have cinema, concerts, dances, television, outings, etc., in addition to any sum granted to them, and to speak of "wages" is ludicrous. The deduction from the facts that only one hospital sends patients out to factory work may be nearly true, but cannot emerge from the survey. I know the one referred to by the authors. This is another.

Finally, Sir, I think the accompanying table will show your annotator that we do our best not to detain young adults who *may* become difficult. These are difficult boys, irrespective of what Section of the Mental Deficiency Act they are admitted under.

Distribution of 53 Hospitalized Male Patients Aged 16–30 Years, I.Q. 70+, by Admission Category and Occupation

	Section of M.D. Act		
	6	8	9
Inside the hospital:			
Maintenance work	6	1	0
Vocational training	9	11	3
Outside the hospital:			
"Protected" daily work ..	5	1	0
Normal daily work	5	6	1
Licence	2	2	1
Total	27	21	5

This accounts for nearly the whole of this group within the hospital. The seven on maintenance work have had to be written off for gross physical or psychological disabilities. The 23 on vocational training are passing through to daily employment and licence. The other 23 are already out at work. Although they all have I.Q.s of over 70, I can assure you that the height of that I.Q. is not directly related to the social value of that work.—I am, etc.,

Chertsey, Surrey. J. M. CRAWFORD.

Appendix in Hernial Sac

SIR,—I would like to add one further case of an appendix in a hernial sac to the several already published in your journal recently.

A woman aged 40 was admitted to hospital complaining of a painful swelling in the right groin. She stated that the swelling had been present intermittently for the previous six years—that it appeared on coughing and straining but was easily reducible. One week prior to admission the swelling reappeared but could not be reduced. On examination she had a round swelling about the size of a hen's egg in the right groin below the inguinal ligament and lateral to the pubic tubercle overlying the saphenous opening. The lump was diagnosed as an early strangulated femoral hernia.

At operation the lump was freed from the surrounding tissues and the sac opened, it then being noticed that the content of the sac was a gangrenous appendix. The inguinal canal was then opened and the neck of the sac freed from above; at the same time the constriction ring in the neck was also divided. The sac was then brought up into the inguinal canal and the appendix and caecum delivered into the wound. The constriction ring in the sac had compressed the appendix about 1 in. (2.5 cm.) from its tip and caused gangrene of its distal one inch. The appendix was removed in the usual manner and the sac ligated and removed.

The patient made an uninterrupted recovery. She was seen recently, and had no recurrence of the hernia.—I am, etc.,

Dublin. WILLIAM A. L. MACGOWAN.

The Lithotomy Position in Obstetrics

SIR,—There is undoubtedly a danger that students in this country may gain the impression that the lithotomy position is best for all operative deliveries by forceps, and still worse that they may be taught to apply forceps only in that position. The reason for this is not far to seek. It is probably true to say that most teachers of obstetrics do at least 10 gynaecological operations to one forceps delivery, and they naturally feel more at home (if such an expression is seemly) with the patient in the lithotomy position. This does not mean that it is wise to teach the general-practitioner obstetricians of the future that it is the safest position for forceps delivery.

Professor T. N. A. Jeffcoate states (*Journal*, October 31, 1953, p. 951) that "the greatest danger of forceps delivery at the present time is anaesthesia, and this danger has, if anything, increased with the introduction of modern anaesthetic agents." He goes on to quote "six maternal deaths associated with forceps delivery in the Liverpool Maternity Hospital during the 15 years preceding 1950," and states that no less than half of these were the result of inhalation of vomit during the induction of general anaesthesia. In the *Journal* of December 12, 1953 (p. 1324), I ventured to ask "whether these patients were in the lithotomy position, which we know Professor Jeffcoate favours for all operative deliveries" (*Journal*, June 10, 1950, p. 1359). As no answer has been forthcoming, it seems reasonable to suppose that the assumption was probably correct. If fatalities from this cause can occur in a well-equipped theatre replete with suction apparatus, oxygen, and all the refinements, how much more dangerous would it be if the same kind of emergency occurred to the general practitioner working, perhaps shorthanded, in an ordinary bedroom without such facilities. There is, too, the undeniable fact that indications for forceps delivery frequently arise unexpectedly and often there has been no time to give the same careful attention to the preparation of the patient for anaesthesia as is possible in a planned operation. It is often not possible, or even desirable, to withhold food from a patient during a prolonged labour.

After more than 30 years of experience of the lateral position (which, as I have pointed out before, becomes semi-prone on an ordinary bed) it is quite inconceivable to me that fatalities from this cause would occur in that position, and virtual freedom from this very real risk far outweighs the minor disadvantages of the lateral position, for they are largely theoretical and in practice do not amount to much. I would grant, of course, that if only local anaesthesia is used there is no objection to the lithotomy position, but it is at least questionable whether this form of anaesthesia will become widely adopted for forceps delivery, at any rate in domiciliary midwifery, and I venture to doubt whether the patient at the end of a long and tiresome labour would be too pleased about it.—I am, etc.,

Mill Hill, N.W.7. A. H. MORLEY.

Dysgerminoma of the Ovary

SIR,—Mr. Maurice Hershman (*Journal*, January 23, p. 198) gives an interesting account of a dysgerminoma of the ovary which had undergone torsion, which he states is the first recorded case of such a condition. In view of its apparent rarity I would like to briefly record a similar case which has recently been under our care.

The patient, an unmarried girl of 21, was admitted to hospital on January 13, 1954, complaining of severe colicky lower abdominal pain and vomiting. She was sweating profusely, temperature 103° F. (39.4° C.), pulse rate 100. A clearly visible, tender swelling was found arising out of the pelvis. Previous menstrual history was normal. On catheterization the bladder was found to be empty. A diagnosis of torsion of an ovarian cyst was made and laparotomy performed through a lower right paramedian incision. Almost the whole of the lower abdomen and pelvis was filled with a solid, lobulated tumour arising from the right ovary. The pedicle had undergone torsion and a commencing area of necrosis was apparent on the superior pole of the tumour to

which great omentum was attached. The tumour was removed without difficulty, the patient making an uninterrupted recovery. Histological examination of the tumour showed it to be a dysgerminoma.

There were no signs of pseudohermaphroditism in this case, and the menstrual history prior to operation had been normal. No signs of intraperitoneal metastasis were evident at operation, and subsequent radiography of the chest revealed no abnormality.—I am, etc.,

Sheffield, 6. BRYAN ROWLANDS.

Fatal Bronchial Asthma

SIR,—I was interested to read the article by Drs. C. Kelman Robertson and K. Sinclair (*Journal*, January 23, p. 187). Sudden death may also occur in an emphysematous patient who has an acute respiratory infection or even on recovery from the infection, and post-mortem examination may not be helpful in deciding the exact cause of death. In some cases, however, I have noticed the presence of a marked cerebellar pressure cone which may, of course, in itself cause sudden death. The cerebellar pressure cone is in keeping with the high C.S.F. pressure seen in these cases. Since long-continued asthma may lead to emphysema I think that this is worth considering as a cause of sudden death in asthma. The difficulty, however, lies in deciding whether a cerebellar pressure cone is abnormal or not, and we are now investigating this.

I should like to issue a word of warning in giving an oxygen–CO_2 mixture to the old-standing asthmatic subject who is suffering from acute anoxia and who will have some degree of CO_2 retention. The inhalation will cause further rise of CO_2 and the production of carbon dioxide narcosis.—I am, etc.,

Enfield, Middlesex. THOMAS SIMPSON.

SIR,—With reference to the article by Drs. C. Kelman Robertson and Kenneth Sinclair (*Journal*, January 23, p. 187), the following five cases of sudden death at the onset of an attack of asthma may be of interest. They occurred in a series of 700 necropsies, two-thirds of which were hospital cases and one-third coroners' cases. In four instances the only clinical history consisted of the policeman's report stating that the patient was a known asthmatic. The fifth case died suddenly in hospital, having previously been brought round from status asthmaticus. Some particulars of these five cases are shown in the following table.

Case No.	Sex	Age	Month of Death	Evidence of Infection	Drugs Taken Soon Before Death
1*	F	31	December	—	—
2*	F	45	September	—	+
3*	F	60	February	+	—
4*	M	33	September	—	—
5	F	36	September	—	+

* Coroners' cases.

All showed characteristic sticky mucus plugging the bronchioles and ballooning the lungs. Though probably of no significance, two of the cases occurred soon after the administration of drugs (Case 2, two aspirins; Case 5, a barbiturate tablet). Case 3 showed an unusual nodule of pneumonic consolidation about 3 cm. in all diameters, close to the hilum of the left lung, which sectioning showed to be a patch of haemorrhagic bronchopneumonia. The speed at which death can occur is remarkable. Case 1 said she felt an attack of asthma coming on, and sent her young son up to the bedroom to get some ephedrine tablets. On his return he found his mother lying dead on the floor.

Regarding the mode of death, I would favour the authors' first suggestion that the heart fails due to increased resistance in the pulmonary bed. The relative infrequency of petechiae of the lung and heart surfaces implies to me that a respiratory struggle against obstruction did not occur.—I am, etc.,

Braintree, Essex. A. I. D. PRENTICE.

Symptoms of Dracunculiasis

SIR,—I have just received my *Journal* of December 12, 1953, and have read "A Case of Dracunculiasis (Guinea-worm) in Nairobi," by Dr. A. L. Ribeiro (p. 1310), with interest. Dr. Ribeiro thought it remarkable that his patient did not show the "usual clinical symptoms such as fever, diarrhoea, vomiting, and urticaria" which are associated with the arrival of the worm to the surface. Before I became a medical student I suffered several times from dracontiasis, and now I am in practice in an area where the disease is endemic. It was only once, and that was my first attack, that I developed a sudden fever and urticaria before the worm made its shocking appearance. On all other occasions all I had was a dull ache followed by intense itching on my leg. This was followed by a blister over the area of itching and soon this burst and I saw one end of the worm.

From experience some of my patients who recognize the aching control their fingers and anxieties, allow the blister to form and burst, and the worm makes its appearance with as little interference as possible. But those who scratch and irritate the area and pull prematurely on the worm, which at first is thin and very delicate, are calling for trouble. The part gets swollen, hot, and tender, with development of fever and, particularly if having the disease for the first time, urticaria; if the patient was foolish enough to get the worm broken then he would have many sleepless nights from a big abscess. My people here, who have had the disease with them for centuries, know all these, and hence "the usual symptoms" expected by Dr. Ribeiro are unusual.—I am, etc.,

Irrua, Nigeria. XTO. G. OKOJIE.

Unwrapping the "Journal"

SIR,—I second the motion made by Dr H. Lyndhurst Duke (*Journal*, December 12, 1953, p. 1326) that the *Journal* reinstate that "ingenious old wrapper" which many a reader cherished and librarians adored.—Hopefully, I am, etc.,

Philadelphia. CATHERINE DELSORDO.

What is a Psychopath?

SIR,—I have noted with interest the discussion which has been carried on in your correspondence columns regarding the definition of a psychopath. May I call your attention to the definition given in the *Psychiatric Word Book*, which was written by the late Dr. Richard H. Hutchings, and which is published by the New York State Hospitals Press? Their definition is as follows: "'Psychopathic Personality.'—A type of personality afflicted with diminished volutional [*sic*] control and heightened emotional response to stimuli."

I am quite sure that this definition could not be improved upon. It is very clear, simple, and practical.—I am, etc.,

Fort William, Ontario. JOHN R. HOWITT.

Weight of British Children

SIR,—The article by Dr. E. M. B. Clements (*Journal*, October 24, 1953, p. 897) concerning heights and weights of schoolchildren, together with the letter by Dr. W. T. C. Berry, Mr. E. R. Bransby, and Mr. W. H. Hammond (*Journal*, December 12, 1953, p. 1324) on the same subject, has been of considerable interest to us. We have recently used data on the heights and weights of over 7,000 Birmingham children attending local authority schools in 1952 to obtain comparisons between children drawn from good, medium, and poor neighbourhoods. The children were of three age groups, the ages at their last birthdays being 6, 11, and 14. The smallest group drawn from any type of neighbourhood was 103 (boys aged 11, from good neighbourhoods). Whilst fairly consistent differences were found in the average heights and weights of both boys and girls coming from the different type of neighbourhoods in each of the three age groups, yet in only certain cases were these differences statistically significant, when a difference of twice the standard error was taken as a level of significance. One

of us (H. M. C.) whilst in Sheffield in 1947 found similar differences, using the same criterion for significance, in a survey amongst schools classified into the three groups. The question of significance seems to be of importance and may account to some extent for the apparent differences in the results of various surveys. Where numbers in the samples are small a greater observed difference is necessary to achieve any conventional level of significance. Other factors accounting for contradictory results are, no doubt, type of school considered and classification system. The classification according to catchment areas of schools is theoretically of very doubtful validity, but in practice seems to yield useful data.

Our results showed significant differences in the heights and weights of both boys and girls at age 6, coming from good and medium neighbourhoods. At the age of 11 only the heights and weights of the girls from these districts were significantly different, and at 14 differences were not significant. In comparing children from medium and poor neighbourhoods, differences in height for both boys and girls at age 6, and in weight at age 14, were significant. There was also a significant difference in the height of girls at age 14. No other differences were significant.

In his article, Dr. Clements states that "to-day, average children of the same age in the middle- and lower-income groups are the same height, while the average child in the upper-income group is about 2 in. taller." If by the term "average child" Dr. Clements requires us in this context to understand "a child of average height," then we should be glad to discover the basis for his statement, since, using the figures given by him in Table I, the mean of the difference in height between boys of average height and age 5–13 from upper- and middle-income groups was found to be 0.64 in., and for girls this difference was 0.65 in. Also, the mean difference in height between boys of middle- and lower-income groups was found to be 0.46 in. and between girls 0.1 in. These figures are more in agreement with our own.

Similarly, while in disagreement with the statement that "weight differences between comparably aged boys of the three income groups have now been eliminated," we do not find our figures to be very different from those given by Clements. The range of differences in weight between comparably aged boys of the upper- and middle-income groups obtained from Table II is 6 lb. to 13.6 lb., while the mean difference is 1.75 lb. Thus the range is greater than that of 1½–6 lb., quoted by Bransby *et al.* for boys aged 5–15 in Sheffield. We find, however, neither in our figures nor in Clements's any progressive increases in weight differences with age to correspond to those quoted for boys of 5, 8, and 12 in Liverpool, attending schools in good and poor neighbourhoods.

Because of the conflicting results obtained by surveys in different towns, and even within the same town with a different system of classification and a different size of sample, it seems important to stress the point that at present any results obtained by surveys such as those considered above provide estimates which relate with certainty only to the local community sampled. To treat that community as a sample of a more widely defined population involves assumptions which have yet to be validated.—We are, etc.,

H. M. COHEN.
K. E. GALES.

Birmingham, 15.

"Status Lymphaticus"

SIR,—Dr. H. B. Dodwell (January 16, p. 149) states that no reference to this syndrome can be found earlier than 1850; it seems, however, that Kopp in 1830 first drew attention to thymic asthma and "thymic death."[1] While one can agree with Dr. Dodwell that status lymphaticus is a hotch-potch of all kinds of cases with low resistance and sudden death, and while thymic compression or "thymic dysendocrinism" as a cause of death most probably does not exist, the syndrome should perhaps not be regarded as a myth in the light of modern medical knowledge. On the contrary, it seems remarkable that this syndrome was conceived as a clinical entity so long ago and on purely anatomical grounds. It would not be the first time that science has detected some truth in an old "myth."

The anatomical findings indicating hyperplasia of lymphoid tissue and persistence or enlargement of the thymus gland appear in an interesting light if one remembers that injection of pituitary corticotrophic hormone and/or adrenal cortical glucosteroids rapidly causes involution and depletion of lymphoid follicles and of the lymphatic and thymus glands. This conspicuous change is accompanied by an increase in the number of circulating lymphocytes and in the urinary excretion of uric acid which is presumably formed by the breakdown of lymphatic nuclei. Other pertinent changes which occur simultaneously are not important for the present argument. However, it seems certain that the amount of lymphoid tissue and its rate of breakdown is regulated by the adrenal cortex via the pituitary. This breakdown occurs as an important physiological response to stress, in the sense of Selye, and seems to form part of the mechanism by which the body is protected against injury and for which an adequately functioning pituitary-adrenocortical system is necessary.

As I have previously suggested,[2] the assumption seems close at hand that decreased resistance to stress in connexion with lymphoid and thymic hyperplasia—i.e., the status thymo-lymphaticus—is an expression of (constitutional ?) pituitary-adrenocortical deficiency in respect of corticotrophin and/or adrenal glucocorticoid secretion, the anatomical findings merely being a consequence of the deficiency but not the cause of the syndrome. This assumption would explain the association of lymphoid hyperplasia with lack of resistance to stress which is known from other endocrine diseases with adrenocortical deficiency (e.g., Addison's, Simmonds's, and Graves's disease). The hypothesis could easily be verified by investigations into the adrenal cortical reserve of cases with suspected status thymo-lymphaticus.—I am, etc.,

London, W.1. H. UCKO.

REFERENCES

[1] Quoted by T. Brugsch (1937). *Lehrbuch der Inneren Medizin.* Berlin and Vienna.
[2] *Endocrine Diagnosis*, 1951, pp. 198 and 304. London.

Penicillin-resistant Gonococci

SIR,—In view of the question which must be exercising the minds of many venereologists whether there is any near danger of gonococci becoming penicillin-resistant, the following case may be interesting.

X.Y.Z. attended the V.D. Department, Central Middlesex Hospital, on the evening of October 23, 1953, with a slight urethral discharge and a history of having been treated the same morning with 600,000 units of penicillin in the form of "distaquaine." No gonococci were found in the discharge and the patient was treated with potassium permanganate irrigations. On November 5 he reattended with a profuse urethral discharge containing gonococci as seen in slide and culture. I personally injected 600,000 units of penicillin in the form of "prolopen."

When he was next seen on November 12, the discharge had disappeared, but on November 19 when he reattended he reported that the discharge had reappeared on November 15; on his reattendances the discharge was profuse, with myriads of gonococci in the smear, more than I have ever seen in a slide in my thirty years' experience. The culture was positive and the gonococci there were reported as sensitive to penicillin. I gave him a mega unit of penicillin in "prolopen" and the discharge again disappeared, but it had returned by December 7.

When I saw him on December 10 gonococci were profuse in smear and the culture was again positive. There was no evidence of infection in the prostate, and, as far as I was able to see later when under local treatment, the inflammation had died down. There seemed to be no closed focus in the anterior urethra.

Under very close cross-examination the patient denied any fresh exposure to infection after the first sign noted above, and I believe him. Is this the writing on the wall ?—I am, etc.,

London, N.W.10. P. A. CLEMENTS.

Carcinoma of Colon and Salmonella Infection

SIR,—This male patient, aged 62 years, was admitted to the hospital on October 24, 1953, with a medical history and diagnosis of a possible subacute intestinal obstruction. In addition, however, he had inflammatory congestive chest symptoms for one week previous to admittance which had not responded well to penicillin.

On admittance he had definite signs of bilateral basal congestion and there was some abdominal distension. He was put on

500,000 units of intramuscular penicillin six-hourly, but his pyrexia continued although his chest symptoms improved. Blood was sent for agglutination reaction on October 30, 1953. A barium enema was done on November 2, 1953, and this confirmed the clinical diagnosis of obstructed large bowel (obstruction was present in mid-third of transverse colon). On November 3, 1953, a laparotomy was performed by me under general anaesthesia, and the patient was found to have a string carcinoma in the mid-third of the transverse colon. There were multiple secondaries in the surrounding glands and the liver was full of nodular secondary growths. A side-to-side anastomosis above and below the obstruction was performed to relieve symptoms of obstruction. Following the operation signs of ileus developed, but these resolved within a day or two. The bowels were functioning normally within three days.

The final pathological report dated November 13, 1953, was: "The organism isolated from this patient's clot culture has been identified by the salmonella reference laboratory as *Salm. anatum*." Following the diagnosis of a salmonella blood infection the patient was treated by chloramphenicol and he eventually responded quite well. When he was discharged home on November 28, 1953, his bowels were functioning satisfactorily, his abdominal wound was well healed, and he was able to get about. Since discharge home, however, he has developed further pyrexia and has required a further course of chloramphenicol.

The interesting point here, however, is the association of salmonella infection with carcinoma of bowel with multiple secondaries. In the past I think that most of us have been of the opinion that the temperature often met with in patients suffering from a carcinoma with multiple secondaries was due to absorption of the breakdown protein products, but this case probably indicates that in some cases, at least, normal protective mechanisms to combat blood infections are thrown out of gear, and it may well be that if blood cultures were performed on such cases some at least might yield a positive blood culture.—I am, etc.,

Oswestry. A. LUTTON.

Disease and the Pig Bin

SIR,—Dr. Kathleen Vaughan's biting fly (*Journal*, January 30, p. 279) is almost certainly *Stomoxys calcitrans L.*, the "biting house fly" or "stable fly." Their habits are consistent with their being able to breed in pig bins, and there is some evidence that they may be able to transmit pathogenic organisms.

These insects have, however, always been common on farms, where they breed on soiled vegetable matter, and one would have expected that their role in disease transmission in country districts would have been uncovered by now. It would be very interesting if Dr. Vaughan could substitute an entomologist's net for her fly-swatter and see if she could recover any pathogens from the stomachs of these flies.—I am, etc.,

London, E.C.1. EDWIN R. NYE.

Student International Clinical Conference

SIR,—The British Medical Students' Association has undertaken once again to organize a Student International Clinical Conference in Great Britain from July 15 to 30, 1954, as an activity of the International Federation of Medical Student Associations. It will be divided into three sections: First, there will be seven days in London, when at least five of the teaching hospitals will give lectures and demonstrations, and visits will be made to places of interest; secondly, three days in Birmingham with visits to hospitals, factories, a film show, and a visit to Stratford-on-Avon; and, finally, four days in Edinburgh, where similar activities are being planned. Our greatest difficulty in organizing an attractive programme is to make it sufficiently cheap to enable foreign students to attend, taking into account the expense of travelling to this country. We are therefore appealing for financial support for the Conference. We hope to raise at least £500, so that we can organize a Conference worthy of what Britain has to offer, and within the student's purse, at the same time repaying in some measure the generous hospitality which British students receive on going to similar courses abroad.

This Association was one of the founder members of I.F.M.S.A., which was set up in 1951 to promote international co-operation between medical students, and at its foundation we were careful to ensure that it would be free of any political activities which seem to predominate in other international student bodies. Its present member countries are Austria, Denmark, Eire, Finland, France, Great Britain, West Germany, Holland, Israel, Norway, South Africa, Spain, Sweden, Yugoslavia. B.M.S.A. was the first chairman nation, and continues to give lead in many fields. The B.M.A., the World Medical Association, and the World Health Organization have expressed sympathy with its ideals. Its aims are strictly limited to promoting and organizing conferences, visits, and exchanges, with some research into student health and education.

There are many foreign students wishing to obtain an insight into British medicine, and we are therefore particularly anxious to make a success of this Conference. I do earnestly hope that your *Journal* can support in this object, and any contributions, however small, will be gratefully received.—I am, etc.,

B.M.A. House, Tavistock Square, London, W.C.1. ALAN B. GILMOUR, President, British Medical Students' Association.

POINTS FROM LETTERS

Polite Surgery

Dr. W. A. J. DONALD (Monifieth, Angus) writes: I am tired of reading about surgical "trauma," surgical "interference," and surgical "aggression." The term surgical "intervention" is more polite and restful to my sensitive, surgical ear.

Requirements for D.T.M.&H. and D.P.H.

Dr. L. R. FLOWERS (Doom Dooma, Assam) writes: By analogy with postgraduate diplomas, such as F.R.C.S., M.R.C.P., D.C.H., D.A., etc., candidates for which are not required to attend a special course but do the requisite amount of work in the respective specialty, I submit that those who have been working for a specified period in the Tropics, dealing with all aspects of tropical medicine and hygiene, should be exempted from the necessity of attending the course for the D.T.M.&H., or the D.P.H., and should be permitted to sit the examination without these preliminaries. This would bring these diplomas into line with all the others, and would eliminate the present factors of time and money spent on a compulsory course, and the resulting unfairness to those who cannot afford these pre-examination requirements.

Measles and Appendicitis

Dr. D. S. BADENOCH (Inverness) writes: Measles is not the only zymotic liable to show up appendicitis in its course. A similar emergency often arises during or following influenza A and B, and indeed many bad colds. The damaging entity common to all is the severe biliary congestion lasting from two to four days. Pathologists have explained, as long ago as thirty years, how the chemistry of the liver comes to a partial standstill, and, in addition, how the flora of the bowel multiplies enormously in the absence of a normal bile flow. If, during the phase of biliary congestion, the patient is fed on converted food, few noticeable sequelae arise. If, on the other hand, he is given fats and starches, he may expect a variety of complications, appendicitis included. Biliary stasis, to my mind, is the commonest cause of acute appendix.

Anaemia and Purchase Tax

Dr. A. PINEY (London, W.1) writes: The only treatment needed in simple iron-deficiency anaemia is administration of an adequate amount of ferrous salt; and the addition of vitamins, folic acid, liver, etc., serves no therapeutic purpose. There seems to be general agreement that ferrous gluconate is less liable to cause gastro-intestinal upset than are other iron compounds. It is therefore amazing that tablets consisting entirely of ferrous gluconate are more expensive than those which contain vitamins in addition to this compound. It appears that H.M. Customs and Excise regard such mixtures as essential drugs, which are therefore exempt from purchase tax, whereas, in fact, this is a stupidity that adds to the size of the drug bill of the N.H.S. and penalizes those patients who prefer to retain their freedom by remaining "private" and paying for their own medicines.

Obituary

O. WYNNE GRIFFITH, O.B.E., L.R.C.P.Ed., J.P.

Dr. O. Wynne Griffith, who died at Pwllheli on January 17 at the age of 97, was one of the oldest medical men in Wales.

Owen Wynne Griffith was born at Nevin, Caernarvonshire, on November 16, 1856. After leaving Bottwnog Grammar School he served as an apprentice with Dr. Evan Roberts, of Penygroes, Caernarvonshire. In his later years he was fond of relating his experiences in those early days, and in 1939 he broadcast some of his recollections. At the age of 17, in 1874, he entered Guy's Hospital as a medical student, and qualified L.R.C.P.&S.Ed. four years later at the age of 21. After qualification he was warned that his health was weak and he took an appointment as a ship surgeon. After two years he returned to Wales and began practice in the Lleyn peninsula of Caernarvonshire, living for most of the time at Pwllheli, where he quickly developed a very large country practice. For the first 25 years of his professional life he travelled many thousands of miles on horseback or in an open gig. He addressed nearly all his patients by their Christian names, and was interested in every aspect of their lives. He had great personal charm and a most lovable nature, and it is doubtful if any man in the district has ever had a warmer place in the hearts of those who knew him. For a long time he was known affectionately all over the district as "the old doctor." Although he officially retired from practice about 20 years ago, he was frequently consulted by his colleagues to the end. When interviewed in 1946 on the occasion of his 90th birthday, Dr. Wynne Griffith was asked for his recipe for longevity. "I'll tell you," he said. "Avoid jealousy: always keep an optimistic view and practise moderation in all things." A member of the British Medical Association for 62 years, he was chairman of the South Caernarvon and Merioneth Division in 1907 and president of the North Wales Branch in 1910–11. He also served on the executive committee of the Division and on the Branch council. In his presidential address to the North Wales Medical Association many years ago he emphasized the need for a ministry of health, and he saw it come into being.

In the life of the community in which he lived Dr. Wynne Griffith was an important figure. He was a member of the Pwllheli town council for over 60 years, an alderman of the borough for 55 years, and mayor for 12 years—a record for the office. He was a founder of Pwllheli Grammar School, and until recently chairman of the governing body. As an appreciation of his services to the town he was given the freedom of the Borough of Pwllheli in 1931. He was also a member of the Caernarvonshire County Council for nearly 60 years, an alderman for nearly 50 years, and chairman of the council in 1921. In his early years he took a keen interest in politics, and at one time was chairman of the Caernarvonshire Liberal Association. He was a personal friend and supporter of Mr. Lloyd George, and had presided at a number of the meetings at which Lloyd George made some of his famous speeches before audiences of about 10,000 people at Caernarvon. Religion played a very important part in his life: he was an elder of the Presbyterian Church for 60 years, moderator of the South Caernarvonshire Presbytery for two years, and a senior deacon of Penmount Church, Pwllheli. In recognition of his public services over many years he was appointed O.B.E. in 1937.

Dr. Wynne Griffith lived a full and happy life, and except for the brief period in his early twenties enjoyed good health until the last two or three months of his life. His cheerful presence will be missed by a large number of friends and acquaintances. He is survived by a daughter and a son, who is a solicitor.

A. E. COOPER, M.D.

Dr. A. E. Cooper, who was for many years consultant anaesthetist to the London, the West London, and the Royal National Orthopaedic Hospitals, died on January 19 at the age of 84.

Austin Edwin Cooper was born at Dublin on February 8, 1869, and was educated at Leeson School and at Trinity College, Dublin. He took the L.M. while at the Rotunda Hospital in 1894, and the degrees of M.B., B.Ch. in the following year, proceeding to the M.D. in 1896. After graduation he held house appointments at the Adelaide Hospital, Dublin, and then came to London to act as resident medical officer at the Pimlico Dispensary. Dr. Cooper was keenly interested in anaesthesia from the start of his professional career. In the controversy which took place in England towards the end of the nineteenth century on the comparative safety of chloroform and ether he was a wholehearted supporter of the use of ether, and so skilled in its use did he become that a certain deep type of anaesthesia was, and still is, named after him by being referred to as "Cooperization." He became anaesthetist to the Royal National Orthopaedic Hospital and assistant anaesthetist to the West London and other hospitals. Later he was appointed anaesthetist and assistant instructor in anaesthesia at the London Hospital and anaesthetist to Poplar Hospital. During the war of 1914–18 he worked in a number of special hospitals for officers, and at the outbreak of the second world war, although retired for some years, he returned to full active work, dividing his time between the London and Whipp's Cross Hospitals. An active member of the Chelsea Clinical Society, he had held office as treasurer and vice-president.

At the hospitals to which he was attached he took an important part in the teaching of anaesthesia, and his willingness at all times to help and instruct students, his unfailing punctuality, and his efficiency and quietness in his work and manner were all admirably unobtrusive qualities which led to his being accepted without full appreciation of his worth until too late—when it was found that an invaluable colleague had gone and a vacancy remained which could never be filled again with the same old-world courtesy and companionship. He was keenly interested in all forms of sport, particularly racing and fishing. In 1898 he married Miss Mary Hunter, and she died in 1946. There were two sons and one daughter of the marriage.

Dr. H. LINCOLN HATCH, who died on November 16, 1953, at the age of 84, was for many years in practice at Pinner. Herbert Lincoln Hatch was born on February 4, 1869, and studied medicine at St. Mary's Hospital, London, qualifying M.R.C.S., L.R.C.P. in 1892. He took the D.P.H. of the English Royal Colleges in 1894, and in the following year

obtained the Durham degrees of M.B., B.S., having passed the intermediate and final M.B. examinations with honours. After qualifications he held house appointments at St. Mary's and at the Hospital for Sick Children, Newcastle-upon-Tyne, and then went to live at Johannesburg, where he was in general practice for a few years. At that time he was particularly interested in the use of x rays in medical practice, and in 1897 read papers on the subject before the Transvaal Medical Society, of which he was the honorary secretary, and the South African Medical Congress: both papers were published in the *South African Medical Journal*. He served as a civil surgeon with the South African Field Force in the Boer War, and then returned to England in 1902, settling in practice at Pinner, where he was for many years a member of the honorary medical staff of the Northwood, Pinner, and District Hospital. A member of the British Medical Association for 58 years, he was chairman of the Harrow Division in 1925–6, and represented his Division at 16 Annual Representative Meetings from 1920 to 1939. He also served on the Central Ethical Committee and its standing subcommittee from 1930 to 1937, the Committee on the Medical Aspects of Abortion from 1934 to 1936, and the Tests for Motor Drivers Committee from 1929 to 1931. During the first world war he served as a captain in the R.A.M.C. from 1914 to 1916, later becoming ophthalmic specialist at No. 4 General Hospital. Dr. Lincoln Hatch had the confidence and affection of his patients and his colleagues, and his presence will be much missed for a long time to come.

Dr. A. P. PIGGOT, formerly deputy medical superintendent of St. James's Hospital, Balham, died on January 6 at the age of 75. Born of an Essex family on April 24, 1878, Allen Pledger Piggot was a medical student at Guy's Hospital and qualified M.R.C.S., L.R.C.P. in 1903. Until 1915 his main interest lay in psychiatry, and he worked in several mental hospitals. Eventually, however, his growing taste for morbid anatomy led him back into the stream of general medicine, and he became an assistant medical officer at St. James's Hospital. From 1916 to 1919 he served as a temporary captain in the R.A.M.C. After demobilization he returned to St. James's, where he became deputy medical superintendent. During the last war he remained at work while the younger doctors joined the Forces, and acted for several years as medical superintendent of the hospital. During his period at St. James's, first under the old board of guardians and later under the auspices of the London County Council, Dr. Piggot saw a gradual transition from old-fashioned Poor Law medical care to modern specialized medicine and surgery. He played a decisive part in gaining for the hospital the outstanding reputation which it now has. He remained mentally active and alert and keenly interested in every new development. His official duties were mainly clinical, in charge of certain medical wards, but, unofficially, he made morbid anatomy his hobby, and performed over 10,000 post-mortem examinations between 1920 and 1950. Overdue to retire in 1946, he was requested by the London County Council to take part in a scheme of research initiated by the Nuffield Foundation on the pathology of old age. Thus it came about that his closing years were spent in placing his vast experience at the service of others, and he was teaching postgraduate students right up to the onset of his last illness. It was during this period that most of his published work appeared. He had previously been joint author of papers on silicosis and on haemopneumothorax. Later he worked up his records on the morbid anatomy of old age, and under his guidance a series of articles dealing with various aspects of the subject were published in the American journal *Geriatrics*. Based as they were on over 2,500 necropsies of subjects over the age of 65, they represent a treasure house of pathology. Cardiovascular disease, new growths (in particular carcinoma of the bronchus), the arteriosclerotic kidney, chronic bronchitis, rheumatoid arthritis—on all these he shed new light. Piggot was always quiet, modest, and unassuming. He sought for no recognition nor expected any reward. Always ready to help a younger colleague, he was the kindly friend of hundreds of doctors and nurses who came in contact with him. Equally at home by the bedside and in the post-mortem room, he was one of the last of those physician-pathologists for whom Guy's is so justly famous. He is survived by a widow, a son, and a daughter, who is following her father's profession.—T. H. H.

Colonel J. M. ELLIOTT, who was for many years consultant venereologist to the Essex County Council, died in London on January 6 at the age of 67. James May Elliott was born on March 16, 1886, and came of a medical family. His father, who was Dr. Haslett Elliott, of Rathfriland, Co. Down, had four sons, three of whom became doctors and the other a dentist. James was the third son. He graduated M.B., Ch.B. at Trinity College, Dublin, in 1910, and after two years in an uncle's practice he joined the Indian Medical Service, later transferring to the R.A.M.C. He served in India, Egypt, and the United Kingdom, retiring in 1937 to take up an appointment as venereologist with the Essex County Council. At the outbreak of the last war he was recalled to the Army and was appointed adviser in dermatology to the British Expeditionary Force in France in 1939–40. After Dunkirk he continued to serve in England until being posted to the Gold Coast, where he became ill and was invalided home. When he ceased to belong to the Regular Army Reserve of Officers in October, 1945, on reaching the age limit, he was granted the rank of colonel. After the war he returned to his position with the Essex County Council, holding the appointment until 1952, when he retired. In the subsequent two years he declined in health very rapidly, and it became apparent that he had never fully recovered from the severe illness contracted on the Gold Coast. His charm of manner and infinite courtesy and kindness to patients and colleagues gave him a large circle of friends, to whom his recent loss of health and his death so soon after his retirement have been a great grief. Colonel Elliott married in 1919 and leaves a widow, a son, and a daughter.—R. H. B.

By the death on January 9 at the age of 79 of Dr. W. J. SUSMAN, Henley-on-Thames has lost a prominent resident and one who played a big part in the public life of the borough for over 40 years. Walter James Susman was born on June 10, 1874, and was educated at Rugby and Caius College, Cambridge, where he obtained a Blue for hockey and narrowly missed a Blue for Rugby football. Even so, he was one of the members of the first English fifteen to play against a French international side. He qualified M.R.C.S., L.R.C.P. from St. George's Hospital in 1900, and took the degrees of M.B., B.Chir. three years later. Among the hospitals at which he held resident appointments were the Middlesex Hospital, the Victoria Hospital for Children, Chelsea, and the Westminster Hospital. In 1903 he entered a partnership at Henley, where he practised until his retirement in 1947. In 1919, after his return from service in the R.A.M.C., he was elected a member of Henley Borough Council and was chairman of the housing committee when an important slum clearance scheme was carried out. The public appointments which he held made an impressive list. In 1925 he became mayor of Henley for the first time. He served a second term as the town's chief citizen during the difficult years of 1945 and 1946. A keen member of the Council for the Preservation of Rural England, he was in addition chairman of the Henley and South Oxfordshire Area Planning Committee from 1935 to 1948, and was a member and vice-chairman of the Henley Area Planning Committee from the time it was formed in 1949 until his retirement from the Council in 1952. He was also chairman of the Henley and District Technical Institute Committee and of the Henley Further Education Committee. He took a close interest in the Henley War Memorial Hospital, to which he was consulting physician, and was a member of its management committee until the introduction of the National Health Service in 1948, when he

became a member of the Reading and District Hospital Management Committee and of the Henley Area Committee. He was a past president of the Reading Pathological Society, chairman of the Reading Division of the British Medical Association in 1919–20, and president of the Oxford and Reading Branch of the Association in 1931. For some years he was deputy coroner for South Oxfordshire. A prominent freemason, he was a member of the Thames Lodge, of which he had been three times master, one of the founders of the Thames Chapter, and a past officer of the supreme grand chapter of England. One of the first members of the Henley Golf Club, he had held the office of captain. In 1914 he married Lena, only daughter of the late Dr. and Mrs. Bransby Brooks, of Sonning, and she survives him. By his death his colleagues have lost the benefit of the experience of a shrewd general practitioner and Henley one who devoted much of his time to the welfare of his fellow townsmen.—N. R. C. L.

Dr. J. W. CRERAR died at Snape, Suffolk, on January 7 at the age of 86. He had been in practice in his home town of Maryport, Cumberland, until eighteen months ago. John William Crerar, the eldest son of Dr. John Crerar, was born at Maryport on November 29, 1867. From Carlisle Grammar School he went on to study medicine at Edinburgh University, where he graduated M.B., C.M., with first-class honours, in 1889, having gained the Vans Dunlop scholarships in physiology and in pathology and surgery in 1887. He became resident surgeon at the Edinburgh Royal Infirmary and demonstrator of anatomy in the university. Owing to the state of his father's health he relinquished his work in Edinburgh and entered the practice at Maryport in 1895. He was a fellow and former president of the Royal Medical Society of Edinburgh, and in 1905 he became a fellow of the Royal College of Surgeons of Edinburgh. During the course of his long life he published several interesting papers in this and other journals. In 1911, for instance, he described in this *Journal* a visit to the Mayo Clinic. A lecture he gave before the Edinburgh Pathological Society in 1918 on the subject of the training of medical students for general practice was later published in the *Edinburgh Medical Journal*. In collaboration with the late Professor J. Lorrain Smith he did some of the experimental work which ultimately resulted in the general use of eusol as an antiseptic during the first world war. Less than a year ago the *British Journal of Ophthalmology* published some historical notes on congenital colour blindness which he wrote jointly with Dr. J. A. Ross. A member of the British Medical Association for 62 years, he played a notable part in local medical affairs. He acted as one of the honorary secretaries of the Section of Pathology and Bacteriology when the Association held its Annual Meeting at Carlisle in 1896. He was also president of the Border Counties Branch in 1912–13; chairman of the English Division in 1910–11, and again from 1924 to 1926; and he represented his Division at a number of Annual Representative Meetings. When he could find time to take part in lay affairs his presence could always be felt in deliberation and decision, and all educational and cultural movements could count on his support. A good deal of his affection was centred upon the Victoria Cottage Hospital, Maryport, from its establishment over half a century ago right up to the time of his death, for he had engaged to be present at the opening of the new out-patient department this month. Always a true son of Maryport, he found great pleasure in collecting material in the form of photographs, maps, and slides showing the history and development of the old port. He traced the home of Isabella Harris, mother of Lord Lister; and in the course of his researches he was able to disprove what had previously been claimed to be a historical fact, that the *Alfred*, the first warship commissioned in the United States Navy, was converted from *The Black Prince*, which was built in Maryport. He discovered that the *Alfred* had been converted from a Philadelphia-built vessel originally called *The Black Prince*, a ship much larger and thirty-two years older than the Maryport vessel. Dr. Crerar was commissioner of the Maryport harbour board, being vice-chairman until his retirement. He was also a justice of the peace for the county of Cumberland for many years. His younger brother, Dr. Charles Crerar, died in Silloth, Cumberland, in 1937.

F. W. C. writes: Dr. J. W. Crerar was the doyen of Cumberland practitioners and only relinquished the chair of the West Cumberland Medical Association after he had given up practice. The parting with him by his colleagues, patients, and the community was very reluctant, and the meeting in his home town, on his going from it after a lifetime's devotion and service, permitted tangible expression by way of a testimonial spontaneously and gladly subscribed, and admitted of things being said in his presence that normally only find their way into an obituary notice. Although he remained unmarried, Dr. Crerar was essentially a family man, the premature death of his father having entirely altered his outlook and the course of his career, bringing him home to his mother, brothers, and sisters. His mother lived to a ripe old age, and it was ever a joy to behold the affection between mother and son. What the lecture room and operating theatre of the larger sphere lost cannot be imagined, but the gain to the home, the general practice, and the community of the small town and countryside was superlative. He slipped quietly out of life without trouble to anyone, just as he would have wished, and we can only express gratitude for a long life lived in altruistic service, and treasure a memory of one who, knowing the struggle of life, ended it as he had always faced it, serenely and with good courage.

Dr. J. M. AHERN, whose death at his home at Kew Gardens on January 12 at the age of 78 will be deeply regretted by his old friends and colleagues, was a member of the prison medical service for nearly 34 years. John Maurice Ahern was born at Glenbrook, Co. Cork, in 1875 and was educated at Belvedere College and at the Royal University of Ireland. He qualified L.R.C.P. & S.I. in 1898 and took the degrees of M.B., B.Ch. three years later. He joined the prison service as deputy medical officer at Liverpool in 1902 and then served successively in that capacity at Parkhurst, Birmingham, and Wakefield until 1917, when he left to enter the R.A.M.C. and saw service in Salonika in the first world war. He returned to his prison duties in 1919, being posted to the Borstal Institution at Rochester, where he acted as deputy governor in addition to his work as medical officer. Within a few months he was promoted to medical officer, class I, and two years later assumed medical charge of the prison at Liverpool. There he soon became a well-known figure in the courts, and his opinion on the mental condition of the prisoners under his care was regarded with respect. In 1930 he left Liverpool to become medical officer at Parkhurst and Camp Hill, where he remained until he retired in 1936. Ahern, however, was still an active man, and in the earlier part of his retirement undertook further medical work, including that of assistant medical officer at various mental hospitals. He was an able clinician and a man of considerable learning and acumen. He had, perhaps, a slightly eccentric personality, but this quality, with his irrepressible witticisms, only served to endear him the more to his colleagues and patients alike. He was for some years a member of the Royal Medico-Psychological Association, and among the papers he wrote were "An Inquiry into the Mentality of Juvenile Adult Delinquents" (1920) and "Certification as a 'Moral Imbecile'" (1925). He was a versatile man who enjoyed his family life and was in his younger days an enthusiast over his hobbies, such as poultry keeping and carpentry. Some of the furniture from his bench was very well made. He married Evelyn, daughter of the Hon. Edwin Reed, and there were two sons of the marriage. Mrs. Ahern died in 1949.—H. K. S.

Dr. ROBERT TINDALL, who was in practice at Hurworth, near Darlington, for over twenty-five years, died at Crofts on-Tees on January 12 at the age of 68. Robert Tindall was born on October 21, 1885, and studied medicine at Aberdeen University, where he graduated M.B., Ch.B. in 1909. After holding house appointments at Aberdeen Royal Infirmary and at Birmingham General Hospital, he was in general practice for two years, first with his uncle, Dr. F. M. Tindall, at Bedlington, and then at Stanhope. In the first world war he served in France for four years with the 27th Field Ambulance, 9th Scottish Division, retiring with the rank of major. He was mentioned in dispatches three times and in 1918 was awarded the Military Cross. In 1919 he settled in general practice at Hurworth-on-Tees, where he made many friends over a wide agricultural and residential district. He was soon accepted as an able, painstaking, and kindly doctor. An excellent diagnostician, he did invaluable work in the community he served and will be long remembered. He also took a prominent part in the life of the village, being chairman of the local district nursing association and of the village hall committee for many years, besides being an active member of the local branch of the British Legion. In the last war he served as medical officer to the 20th battalion of the Home Guard, with headquarters at Darlington, where he was also chairman of a medical board. He was chairman of the Darlington Division of the British Medical Association in 1929–30, and again from 1945 to 1948. While still apparently a robust and tireless man he was struck down in 1946 by a sudden illness, which compelled his retirement, to the great regret of all who knew him. Crippled as he was, he settled quietly at Crofton-Tees and accepted his enforced idleness with more philosophic calm than could have been expected from one who had always been a man of action. He had always been keen on outdoor sports, especially golf and fishing, but he was now condemned to inactivity. He read widely, and constantly fell back on the Waverley novels, which he devoured completely in the first year of his illness. He was a man of decided views, and, though very outspoken, his comments were always enlivened with humour and a racy wit which endeared him to his friends. During his long illness the constant devotion and cheerfulness of his wife were a great solace to him. His elder son, Maxwell, was a major in the Gordon Highlanders and gained the Military Cross in the last war, but was killed at the crossing of the Seine. The only surviving son is Captain Angus Tindall, who is serving in the same regiment in the Regular Army. To him and to Mrs. Tindall we extend our deepest sympathy.—G. G. F.

Dr. LINA MARY POTTER, who died in the German Hospital, London, on January 15, was for something like 40 years a general practitioner in inner North London. She was a woman of marked personality, enthusiastic in a number of causes, and hail-and-well-met to a wide company of friends. In the 'twenties and 'thirties she was prominent in the affairs of the British Medical Association, reaching the chairmanship of the City of London Division and serving as a representative for many years. She was born in 1875, the daughter of a well-known physician in his day, John Baptist Potter, who was on the staff of Westminster Hospital. On her mother's side she was related to the late Dr. Lancelot Burrell, senior physician to the Royal Free. She received her medical training at the London School of Medicine for Women, qualifying in 1910, and she undertook some further studies at the University of Geneva. In the first world war she served with a women's medical unit which went out to Serbia, and seemed to have enjoyed the improvisations and emergencies which such an expedition entailed. She returned with a love for the Balkan country, and only a year or two ago revisited what is now Yugoslavia. She also went to Russia in 1916, and of medical work there on the eve of the revolution she had many strange tales to tell. After her war experiences she settled in general practice in one of the lovely old houses overlooking Highbury Fields, and there, on the fringe of the city, she cultivated a big country garden. She carried out an astonishing amount of work in one form and another. She was on the panel of lecturers for the L.C.C.; she was attached as medical adviser for special cases to Scotland Yard; at one time she was director of the section of child welfare of the League of Red Cross Societies, a work very near her heart; she had great enthusiasm for the St. John Ambulance Brigade, giving lectures and attending committees and parades. At one time she was medical officer to the old Greenwich Union Infirmary. She also found time to contribute to medical literature, mostly on the subject of nutrition and child care. In the British Medical Association Lina Potter was a well-known and respected figure. She had been a member for just over 30 years. In the centenary year of the Association, when the principal gatherings were held in London, she was one of the four vice-presidents of the Metropolitan Counties Branch and vice-chairman of her own City Division, becoming chairman the following year. She was also a keen member of the Medical Women's Federation, and the meetings of the Hunterian Society were not quite complete without her presence, and the more Bohemian they were the better she fitted in. She was a friendly soul as well as something of a "character." To younger women starting practice she was constantly encouraging. She served on the council of Byng Hall, the hall of residence for women students of the University of London. Her circle of friendship included all dogs and cats in her neighbourhood, and her love of animals extended beyond the domestic hearth; she was an active Fellow of the Zoological Society. In recent years she had given up continuous general practice but helped her colleagues as locumtenent. At many medical gatherings in and around the City of London her hearty greeting and veteran gaiety will be sadly missed.

Medico-Legal

ANTIHISTAMINES AND ALCOHOL

A warning about the effects of antihistamine drugs coupled with alcohol was given by Mr. Victor Durand at London Sessions on January 26. He was appearing for Donald Charles Shuter, 49, company director, who pleaded guilty to being under the influence of drink or a drug when in charge of a car. Shuter was fined £15 with 15 guineas costs, and his licence was endorsed, but he was not disqualified from driving.

Mr. Durand said that Shuter, who had been driving for 35 years and had no previous convictions, was allergic to tinned crab, and after eating some developed a skin complaint. His doctor had prescribed antihistamine capsules for Shuter. They were delivered straight from the doctor's surgery. No warning, no qualification, was made save as to the number he should take and the rate at which he should take them. He said that Shuter was a gentleman who did partake of alcohol in moderate quantities, and on this particular night he had taken these capsules between 11 and 11.30 p.m., having already partaken with his wife and a friend of a bottle of wine and before that one pink gin. Although there was no immediate effect, it seemed now quite certain that there was disorientation as a result of the capsules affecting the alcohol.

The doctor said in evidence that the drug magnified considerably the effect of alcohol. He had given Shuter no warning, but he realized now it would be as well to give one, particularly to a motorist.

Mr. Durand, submitting that there were "special circumstances," said that the doctor was rather shaken after Shuter's arrest to find he had landed his patient in a predicament.

Mr. Henry Elam (Deputy Chairman) agreed with the submission and said Shuter would not be disqualified from driving.

Medical Notes in Parliament

A.C.T.H. and Cortisone

In the House of Lords on February 3 Viscount SAMUEL asked the Government whether a patient requiring treatment by A.C.T.H. or cortisone could obtain it if he was registered under the Health Service but not otherwise, and, if so, whether the regulation controlling the supply of these drugs would be altered to remove that discrimination.

Viscount WOOLTON, Chancellor of the Duchy of Lancaster, said the answer was "No," but the Minister of Health was glad of the opportunity to remove any uncertainty. The supply of A.C.T.H. and cortisone was controlled, but there was no question of having to be registered under the Health Service to obtain them. They were recent drugs which could have harmful effects, and experience in them was limited. For that reason they were supplied only to hospitals which had the necessary laboratory facilities and experienced medical staff. That staff enjoyed full discretion in the use of the drugs, which might be given to private or other patients at the hospital. In addition, other doctors or hospitals could obtain supplies from those selected hospitals if the drugs were required to treat one of the conditions in which they might be necessary to save or prolong life. Supplies were available to private patients on payment.

Viscount SAMUEL commented that the information might bring some reassurance to private patients. Viscount WOOLTON added that if Lord Samuel would give him particulars of any specific case he was certain the Minister of Health would be glad to follow it up.

Mortality in Amputees

Brigadier F. MEDLICOTT asked the Minister of Pensions and National Insurance what progress was being made by the investigation into the problem of increasing disablement suffered by limbless ex-Service men as they get older. Brigadier J. G. SMYTH, Parliamentary Secretary, stated on February 1 that the vast majority of the medical examinations requested by the Rock Carling Committee (see *Journal*, March 28, 1953, p. 717) had been concluded, and it was hoped to clear the small remainder in the next fortnight or so. The clinical findings relating to over 5,000 concluded cases were being collated, and the results would be sent to the committee for consideration as soon as possible. The Minister would prefer not to prophesy when the investigations, which were of international importance, would be completed. When the final report of the committee was available he proposed to study it in consultation with his principal medical advisers and subsequently with his Central Advisory Committee.

Amputation and Arteriosclerosis

Mrs. B. CASTLE on February 1 asked the Minister of Pensions and National Insurance why, in view of the independent and responsible medical opinion submitted to him in support of the application by Mr. Aaron Barnes, of Blackburn, for an increased war pension in respect of the amputation of his second leg, he had failed to give this applicant the benefit of the reasonable doubt which existed in his case. Brigadier J. G. SMYTH, the Parliamentary Secretary, stated that the consensus of expert medical opinion left no room for reasonable doubt that the amputation of Mr. Barnes's right leg in 1953 was not connected with the loss of the left leg in 1917. Mrs. CASTLE said that she had sent the Minister a report by an independent specialist of high repute that the degeneration of Mr. Barnes's right leg might have been associated with the first amputation. Brigadier SMYTH said he had read the reports of the two medical men Mrs. Castle had sent, and they were very indefinite, just indicating that it was worth making a claim. During the past seven years the Ministry had heard of only two cases in which it was claimed that arteriosclerosis arose in a sound limb as a result of wearing an artificial limb. One of these cases, exactly similar to that of Mr. Barnes, was referred to two independent medical experts, both of whom confirmed the wealth of medical opinion in the Ministry on these cases, that the wearing of an artificial limb would not cause, aggravate, or precipitate the onset of arteriosclerosis in the sound limb, and that the incidence of arteriosclerosis was certainly no greater among amputees than among civilians who had no wounds.

Nutritional Value of Margarine

Mr. R. W. SORENSEN asked the Minister of Food what were the main oils used in the manufacture of margarine; what were their respective food values; to what extent vitamins were added in the course of manufacture; and the respective nutritional merits of one pound of standard margarine and butter. Major LLOYD-GEORGE gave him the following information on February 1: The main oils used in the manufacture of margarine are coconut, palm kernel, palm, and groundnut oils, which are of similar food value. Margarine sold for domestic purposes contains 450–550 international units of vitamin A and 90 international units of vitamin D per ounce. Vitamins are not added to margarine used for manufacture. The fat content and energy value of butter and margarine are almost the same. The vitamin content of butter varies with place of origin and season of production. An average vitamin A value is 14,000 international units per lb. compared with 8,000 in special margarine, and an average vitamin D value is 270 international units per lb. compared with 1,440 in special margarine.

Mr. SORENSEN asked what was likely to be the standard form of margarine available, and if the Minister would consider placing on the labels of margarines some indication of their nutritional value. Major LLOYD-GEORGE said that after de-rationing better-quality margarine would be available, and there would also be a margarine the same as the standard margarine used to-day. He would look into the point about labels.

Acidity in Soft Drinks

Dr. BARNET STROSS returned to his charge that the acidity of "Cola" drinks was harmful (see *Journal*, February 6, p. 340), and supported it with the results of American investigations. Dr. McCay, who was professor of nutrition at Cornell University, New York, had stated in evidence before a Congress Committee in 1950 that human teeth immersed for two days in Coca-Cola became very soft. That, Dr. Stross said, he had proved for himself, with teeth provided for the experiments by two other M.P.s. Professor McCay had also deplored the use of carbonated drinks which were so acid, not only because of damage to teeth, but also because of peptic ulceration, and in the case of children because of the caffeine content. Dr. Stross said that he had not picked out Coca-Cola to make any specific attack on it alone. Other drinks—for example, apple juice, grape juice, sweetened grapefruit juices—had a high acidity, *p*H 3.1, which meant there was a risk of teeth erosion if they were taken in excess over a long period.

Dr. CHARLES HILL, Parliamentary Secretary, Ministry of Food, said that evidence had been produced that extracted human teeth left in Coca-Cola for 72 hours had lost weight due to the attack on the calcium. They were expected to infer that in the swift passage of acid drinks through the lips and down the throat there was likely to be comparable danger. Had the fluid used been fresh lemon juice the loss of weight would not have been 5 to 10%, but 35%. Had it been grapefruit juice, orange juice, a neutral solution of citrate, or even distilled water, there would have been a loss of weight. These teeth were extracted; there was no protective layer of mucin, no washing by alkaline salivary

juices. Such experiments were of little value either in determining the fortitude of the teeth or the power of the solution. As for the experiments on rats, to make a comparison with an adult one would have to conceive that an adult man drank 25 bottles of Cola a day.

The lower the *p*H below 7 the higher the acidity, and the assumption was that because the *p*H was 2.6 there was particular danger from this kind of drink. The Government chemist had worked out for him the *p*H values of other drinks. Orange barley was 3 in a dilution of one in three, lime juice cordial 2.8, lemon squash 2.75, grapefruit 2.7, orange squash 2.95. After investigations in this country it was reported to the Food Standards Committee in 1951 that British fruit cordials and squashes diluted with four parts of water as usually drunk had a greater erosive action than phosphoric acid drinks.

Dr. Hill did not exclude the possibility of publishing the formula of Cola drinks on the label, although when that was demanded for patent medicines the chemical formula on the labels conveyed nothing to the public except a sense of importance that was aroused in some people when they believed they were taking an unusually complicated medicine. The Food Standards Committee were going to scrutinize the ingredients and acidity of soft drinks generally, not from fear of danger to people's teeth but as a matter of routine because the Food Standards Order was out of date.

Byssinosis Experiments

Mr. H. BOARDMAN asked the Minister of Labour on February 2 how far progress was being made towards the prevention of byssinosis among workers in cotton mills. Mr. HAROLD WATKINSON, the Parliamentary Secretary, informed him that extensive research had been carried out for some years into the problem of preventing the emission of dust in cotton mills which might cause byssinosis. This had been done under the auspices of a joint committee appointed by the Chief Inspector of Factories, with assistance from the Shirley Institute and individual cotton mills. Some progress had been made, though the problem had not been finally solved. Improved methods of dust exhaustion were the subject of further experiment to determine their suitability for general application.

Mental Patients.—The numbers of persons detained in mental hospitals, homes, and hostels at December 31, 1952, were: voluntary 31,402 (10,518), temporary 332 (484), certified 117,407 (152,624). The equivalent figures for 1939 are shown in brackets.

The Acute Rheumatism Regulations, 1953.—In reply to a question about these regulations the Minister of Health explained that their purpose was to assess the value of notification of acute rheumatism and of other procedures of medical interest in the prevention and management of rheumatic heart disease. The areas selected for notification constituted a sufficient sample for this purpose.

Occupational Health Service.—When asked if the Minister of Labour had considered the views received from the National Joint Advisory Council on the subject of a comprehensive occupational health service Mr. Harold Watkinson, the Parliamentary Secretary, said the Minister had received separately from the parties on the council their views on matters arising out of the Dale report on the industrial health services. In the course of these observations proposals had been put forward relating to the development of a comprehensive occupational health service, and this was under active consideration.

Old Age Pensioners' Prescriptions.—The Minister of Health, replying to a question about the cost of supplying medicines to old age pensioners free of the prescription charge, said that many old age pensioners were already entitled to have the charges for prescriptions refunded. It was estimated that the additional cost of relieving all old age pensioners of these charges would be of the order of £900,000 a year.

Agene.—Asked when a decision was likely to be reached on a substitute for agene in flour, Major Lloyd-George stated that everything was being done to expedite the matter. Experiments were involved which had to be watched with great care.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 23** (No. 3) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	18	0	9	0		19	2	9	0	
Dysentery	490	100	178	18	2	419	33	128		
Encephalitis, acute	4	1	1	0		7	1	0	0	
Enteric fever:										
Typhoid	3	0	0	1		3	0	1	0	
Paratyphoid	4	0	0	0		8	1	2(B)	0	
Food-poisoning	148	17		0		62	5		0	
Infective enteritis or diarrhoea under 2 years				17	19				5	11
Measles*	1,106	12	43	31	132	21,882	1349	232	75	
Meningococcal infection	43	5	12	2	3	38	2	18	3	2
Ophthalmia neonatorum	28	0	2	0		28	0	5	1	
Pneumonia†	809	44	323	3	5	1,349	95	242	26	3
Poliomyelitis, acute:										
Paralytic	30	1	6	0	5	15	2	2	0	
Non-paralytic	7	1				9	0			
Puerperal fever§	257	24	12	1	2	265	50	14	2	0
Scarlet fever	1,138	51	181	44	29	1,832	103	297	50	55
Tuberculosis:										
Respiratory	741	72	145	19				145	32	
Non-respiratory	92	6	20	3				24	3	
Whooping-cough	2,357	85	404	49	68	2,792	143	200	28	139

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0	0	0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	1	1	0	0	7	1	3	1	
Influenza	31	4	5	1	2	132	25	2	0	1
Measles		0	0	0	0		1	1	0	0
Meningococcal infection		2	0				1	1		
Pneumonia	356	52	37	14	13	548	116	23	11	12
Poliomyelitis, acute	5	0			0	4	0			1
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	123	17	13	1	5	161	29	20	1	7
Non-respiratory		0	3	0	2		1	2	0	0
Whooping-cough	2	0	1	0	0		1	0	1	1
Deaths 0–1 year	279	34	41	17	12	280	32	40	12	10
Deaths (excluding stillbirths)	6,568	970	734	133	189	7,878	1433	699	129	191
LIVE BIRTHS	7,632	1148	918	214	370	7,508	1110	919	183	345
STILLBIRTHS	206	21	17			192	28	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Food-poisoning in England and Wales

An analysis[1] of reports obtained from medical officers of health and bacteriologists shows that 5,797 cases of food-poisoning were reported to the Registrar-General's office in 1951 and 5,885 in 1952. But the reports show that there were in fact over 11,000 cases in each of the two years; it seems likely that the true numbers are much higher. During the two years there were 715 outbreaks (two or more related cases in different families), 627 family outbreaks (two or more cases in one family), and 5,524 unrelated or sporadic cases. Salmonellae were isolated from 57% of the sporadic cases, from 34% of the outbreaks, and from 62% of the family outbreaks. The source was unknown in 43% of the sporadic cases, in 47% of the outbreaks, and in 28% of the family outbreaks. *Salmonella typhi-murium* was responsible for 2,804 (41%) of the incidents and had a peak incidence in the third quarter of each year. In the two years 69 deaths were reported, 65 due to salmonella infections, 2 probably due to *Cl. welchii*, and 1 to *Staph. aureus*; in one the causal organism was not found.

In only 509 of the 1,342 outbreaks and family outbreaks was the vehicle of infection reported, so that conclusions on the relative importance of different foods cannot be made. The percentage distribution of the various foods concerned in the 509 outbreaks was 66.4 for meat, 9.0 for sweetmeats, 7.9 for fish, 7.1 for eggs (mainly duck eggs), 2.9 for milk, 2.4 for vegetables, 2.4 for fruit, 1.0 for cheese, 1.0 for other forms of food. Processed and made-up meat foods were responsible for 76.3% of the cases attributed to meat.

The largest outbreaks due to milk were as follows: 600 children in Chard U.D., unpasteurized tuberculin-tested milk infected with *Salm. dublin*; 200 children in Stoke Newington M.B., unpasteurized tuberculin-tested milk infected with *Staph. aureus*; 126 children in Lincolnshire, accredited milk and causal agent not found, but staphylococcal contamination suspected; 75 people in Whitby R.D., *Staph. aureus*.

In 243 of the 636 outbreaks in which the general public were involved the place where the food was obtained or eaten was given. Of these outbreaks 129 originated in canteens (85 of them school canteens); 39 in restaurants, hotels, cafés, etc.; 31 in various institutions; 28 in food shops; and 16 in private parties, hostels, etc. Salmonella infections were the causal agent in 14% of these outbreaks. In the 79 hospital outbreaks salmonellae were responsible for 73% of the cases.

The review of the 1951 and 1952 reports on food-poisoning shows that little or no headway has been made in the campaign for clean food. Processed and made-up meat foods account for more than one-half of the outbreaks, and the report suggests that manufacturers and caterers might respond to practical demonstrations better than to theoretical advice in lectures and publications. Duck eggs present a problem that needs some consideration, and it is suggested that they should be used only in foods which are submitted to a temperature of 100° C. for 10 minutes, or boiled for this length of time.

Infectious Diseases

The number of notifications of infectious diseases in England and Wales during the week ending January 23 increased by 223 for scarlet fever, from 915 to 1,138, and 112 for dysentery, from 378 to 490, and decreased by 154 for acute pneumonia, from 963 to 809, and 44 for measles, from 1,150 to 1,106.

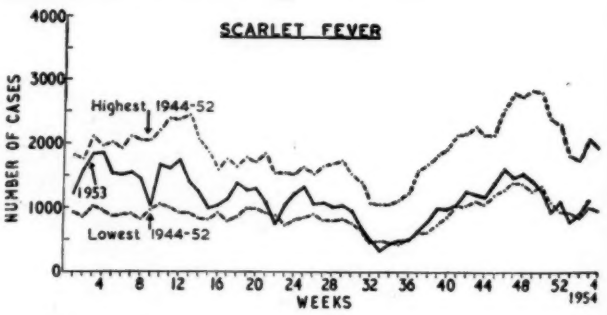
The largest variation in the local trends of scarlet fever was a rise of 35 in Lancashire, from 125 to 160. 2,357 cases of whooping-cough were notified, being 9 fewer than in the preceding week. The largest rises were 40 in Leicestershire, from 29 to 69, and 32 in Kent, from 93 to 125, and the largest falls were 44 in Warwickshire, from 187 to 143, and 36 in Hertfordshire, from 55 to 19. 18 cases of diphtheria, 3 fewer than in the preceding week, were notified; 9 of these cases were notified in Lancashire (Liverpool C.B. 8). Other areas with multiple notifications were Birmingham C.B. 3, West Ham C.B. 2, and Middlesbrough C.B. 2. The largest fluctuations in the incidence of measles were a rise of 89 in Cumberland, from 107 to 196, and falls of 76 in Staffordshire, from 204 to 128, and 33 in Surrey, from 76 to 43. The chief centres of measles in Cumberland were Whitehaven M.B. 93 and Ennerdale R.D. 72.

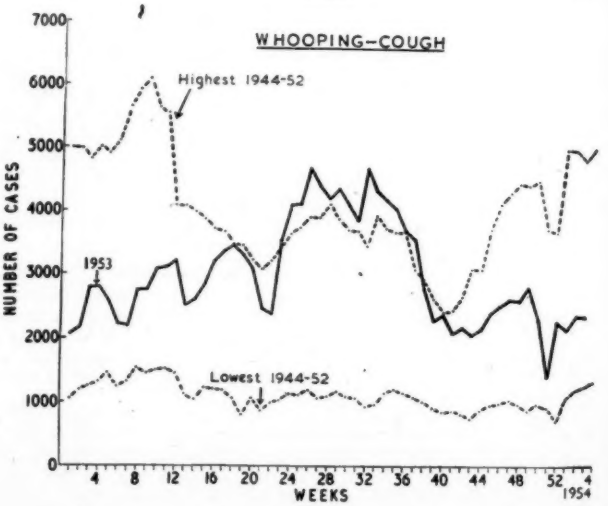
37 cases of acute poliomyelitis were notified. These were 3 more for paralytic and 6 fewer for non-paralytic cases than in the preceding week. The largest returns were Gloucestershire 8 (Bristol C.B. 3), Cornwall 3, Durham 3, Essex 3, and Lancashire 3.

The large rise in the notifications of dysentery was due to increases in existing outbreaks rather than to new centres of infection. The largest returns were Lancashire 121 (Swinton and Pendlebury M.B. 42, Bolton C.B. 20, Liverpool C.B. 11), London 100 (Islington 30, Shoreditch 12), Yorkshire West Riding 70 (Bradford C.B. 22, Leeds C.B. 14), Middlesex 62 (Hendon M.B. 16, Enfield U.D. 10), Sussex 17 (Hailsham R.D. 15), and Warwickshire 16 (Birmingham C.B. 16). The 178 cases in Scotland were notified in 16 areas: the largest returns were Glasgow 101 and Edinburgh 20.

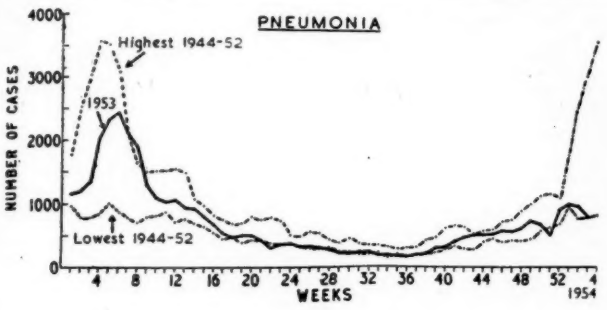
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - - -, the figures for 1953–4 thus ————. Except for the curves showing notifications in 1953–4, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





[1] *Monthly Bull. Minist. Hlth (Lond.)*, January, 1954.



Week Ending January 30

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,058, whooping-cough 2,240, diphtheria 16, measles 1,190, dysentery 572, acute poliomyelitis 22, paratyphoid fever 3, and typhoid fever 1.

Medical News

General-practitioner Research.—An investigation into the value of prophylactic antibiotics or sulphonamides in measles is the first piece of group research being undertaken by the College of General Practitioners, according to the College's "Research Newsletter No. 2" in the current issue of the *Practitioner*. Participation in this research is open to all those on the College's research register. In September an outbreak of an unidentified P.U.O. at Shere, in Surrey, allowed a trial of the "epidemic observation scheme." Those on the register were put on the alert, with the result that similar outbreaks were reported from other parts of the country and the progress of the epidemic was mapped. The Public Health Laboratory Service co-operated by carrying out virus studies on serum and faeces from some of the cases. In order to define the types of illness most likely to repay study by co-ordinated general-practitioner research, with the help of the Registrar-General's Department a survey of the nation's health is being planned. The idea is to analyse a representative sample of morbidity statistics collected over a year or more by general practitioners. In addition to these major schemes, the research register, in which the research interests of each member are recorded, is bringing together doctors with the same problems, and study groups are being formed. Three subjects are noted as particularly appropriate for group study—respiratory tract diseases, hereditary diseases, and psychosomatic disease. A recorder has been appointed to each group: Dr. John Fry (Beckenham), Dr. R. S. Yager (Scunthorpe), and Dr. K. M. Hay (Birmingham), respectively.

Darling Foundation Prize.—At the seventh World Health Assembly later this year Professor George Macdonald and Dr. G. Robert Coatney will receive jointly the Darling Foundation Prize (1,000 Swiss francs and a bronze medal) for their work on malaria. Professor Macdonald is director of the Ross Institute of Tropical Hygiene in London and is distinguished for his work on the epidemiology of malaria. Dr. Coatney, from Bethesda, U.S.A., is noted for his researches on antimalarial drugs.

H. M. Vernon Prize.—Dr. N. H. Mackworth, director of the Medical Research Council's Unit for Research in Applied Psychology at Cambridge, has become the first recipient of the H. M. Vernon Prize. The prize, which is from funds bequeathed by Dr. H. M. Vernon—himself a well-known worker in the field of industrial psychology—is to be awarded biennially by the council of the National Institute of Industrial Psychology for the most valuable research work in industrial psychology and physiology done by a British worker under 45 years of age. Dr. Mackworth is particularly noted for his studies on the effects of climatic conditions on human behaviour.

Medical Press Congress.—The first congress of the Union Internationale de la Presse Médicale will be held in Turin on May 30 under the presidency of Professor T. Oliaro, director of *Minerva Medica*. Among the subjects already chosen for discussion are the question of abstracts of scientific papers, relations between the Press and the medical profession, the place of the film and microfilm in spreading medical knowledge, and the provision of medical news for the lay public. Papers will be presented by Professor L. Justin-Besançon (*Semaine des Hôpitaux*), Dr. A. Plichet (*Presse Médicale*), and Dr. H. Fiessinger. Other subjects will be announced later. Five prizes of 100,000 lire (£57) each will be presented during the congress for the best original papers to have appeared during the years 1952 and 1953 in journals belonging to the Union. Entries for these prizes must be sent in duplicate to Segretaria Generale del Congresso Internazionale della Stampa Medica, Corso Bramante, 83, Turin, Italy.

Rebuilding of St. Giles' Hospital, Camberwell.—The Minister of Health, Mr. Iain Macleod, opened a new operating suite at St. Giles' Hospital, Camberwell, on February 4. The hospital was severely damaged by bombing during the war, so that its pre-war complement of 800 beds is now barely 350. The first stage of the rebuilding, costing £75,000, is the erection of the new operating theatres and the complete renewal of the administration block. It is expected that a further £75,000 will be needed to replace the other damaged buildings.

Royal Commission on Mental Certification and Detention.—Three weeks ago we announced the appointment of Lord Percy of Newcastle as chairman of the Commission (January 23, p. 221). Now the Prime Minister has given the names of the members. The medical members are Sir Russell Brain, P.R.C.P.; Dr. T. P. Rees, medical superintendent, Warlingham Park Hospital; Dr. D. H. H. Thomas, medical superintendent, Cell Barnes Hospital, St. Albans; and Dr. J. G. Wilson, M.O.H. of Cardiff. The lay members are Mrs. E. D. Adrian (wife of Dr. E. D. Adrian, P.R.S.); Mr. Claude Bartlett, president of the Confederation of Health Service Employees; Mrs. Braddock, M.P.; Mr. H. Hylton-Foster, Q.C., M.P.; Mr. R. M. Jackson, LL.D., Reader in Public Law, Cambridge; and Sir Cecil Oakes, member of the Central Health Services Council. The secretary of the Commission is Miss H. M. Hedley, Ministry of Health, 23, Savile Row, London, W.1.

French Government Exchange Scholarships.—Under the terms of a reciprocal arrangement with the Centre National de la Recherche Scientifique, the Medical Research Council invites applications from British workers in medical science, excluding clinical medicine, for two scholarships tenable at research institutions in France during the academic year 1954–5. The scheme is intended for young graduates in medicine or science who have already had some experience in a branch of medical science. Further details and forms of application may be obtained from the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1. The last date for applications is March 31.

Chesterfield Medal.—Inquiries about the examination for the Chesterfield Medal (in dermatology) should be made to the Dean, Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.2, without delay. The closing date for entries is February 28.

Sir Macfarlane Burnet, F.R.S., director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, has left Australia to take part in the Paul Ehrlich and von Behring centenary celebrations at Frankfurt. While there he will receive a von Behring Medal and prize for his work on virus diseases.

Professor John Yudkin has been appointed to the University Chair of Nutrition tenable at Queen Elizabeth College, London.

Mr. William Doolin, Editor of the *Irish Journal of Medical Science* and of the *Journal of the Irish Medical Association,* has been appointed Professor of the History of Medicine in University College, Dublin.

Mr. G. A. Mason, Lecturer in Thoracic Surgery at King's College, Newcastle-upon-Tyne, has gone to Germany for a few days, under the Foreign University Interchange Scheme, to lecture at the Justus Liebig-Hochschule, Giessen.

COMING EVENTS

Professor A. W. Woodruff will deliver the Goulstonian Lectures on February 23 and 25 at 5 p.m. at the Royal College of Physicians. His subject is "The Natural History of Anaemia associated with Protein Malnutrition."

Dr. T. Cecil Gray will deliver the Joseph Clover Lecture at the Royal College of Surgeons, Lincoln's Inn Fields, on March 17 at 5 p.m. His subject is "Disintegration of the Nervous System."

Fourth International Course in Criminology.—This course, organized by the International Society of Criminology with the support of Unesco, will be held in London from March 24 to April 13 under the direction of Dr. Denis Carroll and Dr. Hermann Mannheim. The subject will be "Recent Advances in the Study and Treatment of Offenders." Applications to attend the course should be made at once to "Fourth International Course in Criminology," c/o I.S.T.D., 8, Bourdon Street, Davies Street, London, W.1. The fee is £7.

Week-end Course on the Rheumatic Diseases.—A course with lectures, ward rounds, and practical demonstrations will be held at the Rheumatism Unit of St. Stephen's Hospital, Fulham Road, London, S.W.10, on March 27 and 28. Further particulars may be obtained from the secretary, Fellowship of Postgraduate Medicine, 60, Portland Place, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, February 15

LONDON UNIVERSITY.—At Physiology Theatre, University College, 5.30 p.m., special university lecture in Biochemistry by Professor C. Fromageot (Paris): Metabolism of Sulphur Amino Acids and the Cycle of Sulphur in Nature.

MEDICAL SOCIETY OF LONDON.—8.30 p.m., First Lettsomian Lecture, by Mr. N. C. Tanner: Surgery of Peptic Ulceration and its Complications.

Tuesday, February 16

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. C. C. Chesterman: Antimalarial Drugs—Their Action in Different Stages of the Malaria Parasite in Man.

EUGENICS SOCIETY.—At 26, Portland Place, W., 5 p.m., Galton Lecture by Professor F. A. E. Crew, F.R.S.: Eugenic Appraisal of the Welfare State.

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Dr. James H. Cyriax: Lumbar Disk Lesions.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: Ano-genital Pruritus.

MANCHESTER MEDICAL SOCIETY.—At Medical School, Manchester University, 4.30 p.m., university lecture on the History of Medicine by Dr. Hugh Sinclair: Importance of Boerhaave in the Development of Medical Science.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. R. K. Bowes: Clinical Significance of Amenorrhoea.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Dr. J. Barrie Murray: Chronic Dyspeptic.

Wednesday, February 17

●HARVEIAN SOCIETY OF LONDON.—At Hammersmith Hospital, 8 p.m., clinical meeting.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Benign Tumours of the Corium.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. J. F. Barrington: Indications for the Treatment in Enlarged Prostate.

●LONDON UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES and ATOMIC SCIENTISTS' ASSOCIATION.—At Beveridge Hall, Senate House, 7 p.m., Dr. E. E. Pochin: Medical Uses of Atomic Energy.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Ashford Hospital, 3 p.m., clinical meeting; 4.45 p.m., Dr. K. D. Keele: Pain Sensitivity in Relationship to Clinical Syndromes.

MIDLAND MEDICAL SOCIETY.—At Queen Elizabeth Hospital, Birmingham, 8.15 p.m., clinical meeting.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Sir Geoffrey Jefferson, F.R.S.: Neurology of the Trigeminal Nerve.

ROYAL MICROSCOPICAL SOCIETY.—5.30 p.m., Dr. R. G. White: Microscopy of Antigens and Antibodies within Tissues by the Use of Fluorescent Antibody.

Thursday, February 18

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Dr. W. M. Levitt: Large Volume Radiotherapy; Dr. R. Bodley Scott: Large Volume Irradiation—A Physician's Assessment.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. P. M. D'Arcy Hart: Chemotherapy of Tuberculosis.

CAMBRIDGE UNIVERSITY.—At Zoological Laboratory, Downing Street, Cambridge, 5 p.m., Dr. R. R. Race, F.R.S.: Blood Groups and Their Inheritance.

EDINBURGH CLINICAL CLUB.—At 7, Drumsheugh Gardens, 8 p.m., Mr. G. A. Pollock: Surgical Osteoarthritis of the Hip Joint.

●INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr. Barbara Woodhead: Advice in the Infant Welfare Clinic.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. J. D. Hay: Diagnosis of Congenital Heart Disease; Dr. H. G. Farquhar: Congenital Heart Disease in Infancy.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Professor W. C. W. Nixon: Physiological and Clinical Aspects of Uterine Action.

LONDON UNIVERSITY.—At Wright-Fleming Institute Lecture Theatre, St. Mary's Hospital Medical School, 5 p.m., special university lecture in medicine by Professor L. J. Witts: Changes in the Alimentary Tract in Anaemia.

NORTH-WESTERN TUBERCULOSIS SOCIETY.—At Manchester Royal Infirmary, 5 p.m., Professor F. R. G. Heaf: Present Position of B.C.G. Vaccination.

OXFORD UNIVERSITY.—At Southfield School, Glanville Road, Cowley Road, Oxford, 8 p.m., Dr. A. G. M. Weddell: Science and Medicine.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, W., 7.30 p.m., Dr. M. G. P. Stoker and Dr. B. P. Marmion: Clinical Picture and Epidemiology of Q Fever. A discussion will follow.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. R. Coope: Tuberculous Enlargement of Intrathoracic Lymph Nodes.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., psychiatry demonstration by Dr. D. Curran.

Friday, February 19

BRITISH INSTITUTE OF RADIOLOGY.—5 p.m., meeting of medical members.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4 p.m., Radiotherapy Section Meeting. Dr. T. P. Fox: The Art of the Article.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. S. C. Gold: Lupus Erythematosus.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

LEEDS AND WEST RIDING MEDICO-CHIRURGICAL SOCIETY.—Sir Geoffrey Jefferson, F.R.S.: When Has Headache a Special Significance?

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. J. C. B. Hindenach: Congenital Dysplasia of the Hip.

●ROYAL INSTITUTION.—9 p.m., Dr. Karl T. Compton, D.Sc., Ph.D., LL.D. (Massachusetts): High Voltage for Cancer Therapy and Food Sterilization.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dissertation by Mr. J. A. Stewart: Mitral Valvotomy.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., Public Lecture by Dr. W. S. Feldberg, F.R.S.: On Some Physiological Aspects of Histamine.

Saturday, February 20

BIOCHEMICAL SOCIETY.—At London School of Hygiene and Tropical Medicine, 11 a.m., symposium: Chemical Pathology of Animal Pigments.

APPOINTMENTS

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—A. S. Crawford, M.D., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist, A. Nelson-Jones, M.D., M.R.C.P., Part-time Consultant Physician, and F. R. Sutton, M.B., B.S., F.R.C.S., Part-time Consultant Surgeon, all at Rush Green Hospital, Romford; D. P. Choyce, M.B., B.S., F.R.C.S., D.O.M.S., Part-time Consultant Ophthalmic Surgeon, Southend General, Rochford General, and Runwell Hospitals and Southend Eye Clinic; H. W. Holland, M.B., B.S., M.R.C.P., D.M.R.D., Part-time Consultant Radiologist, Chelmsford Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Ostlere.—On February 3, 1954, at Oxford, to Mary Ostlere (formerly Pattern), M.B., M.R.C.P.Ed., D.A., wife of Gordon S. Ostlere, M.B., B.Chir., D.A., a son.

DEATHS

Ahern.—On January 12, 1954, John Maurice Ahern, M.B., B.Ch., of 10, Ennerdale Road, Kew Gardens, Surrey, late of Liverpool, and Parkhurst, Isle of Wight.

Boyd.—On January 6, 1954, in hospital, James Wood Boyd, M.B., C.M., of 7, Carwinshoch View, Ayr, late of Fallowfield, Manchester, aged 84.

Brims.—On January 13, 1954, Donald Brims, M.B., Ch.B., of 106, West Savile Terrace, Edinburgh.

Edwards.—On January 15, 1954, at Huntington Court, Kington, Herefordshire, Charles Derwent Edwards, M.C., M.D., D.P.H.

Evans.—On January 14, 1954, at Green Hill, Carmarthen, Walter Stuart Evans, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired, aged 64.

Ferguson.—On January 14, 1954, at St. Davids Wing, Royal Northern Hospital, London, N., Thomas Ferguson, D.S.O., M.B., Ch.B.

Fielder.—On January 11, 1954, at Cranwell, Rusthall, Tunbridge Wells, Kent, Frederick John Fielder, M.D., late of Lockerbie, Brixton Hill, London, S.W., aged 83.

Geoghegan.—On January 15, 1954, at the Churchill Hospital, Oxford, Basil Geoghegan, M.R.C.S., L.R.C.P., Surgeon Lieutenant-Commander, R.N.

Glanville.—On January 15, 1954, at North Street House, Emsworth, Hants, Llewellyn Stanley Howard Glanville, M.D.

Hill.—On January 16, 1954, at the War Memorial Hospital, Selby, Yorks, William Bertram Hill, M.D., D.P.H., of 14, Leeds Road, Selby, aged 74.

Salter.—On January 5, 1954, in hospital, Mombasa, Charles Edward Salter, M.D., F.R.C.S., of Nairobi, Kenya, late of Scarborough, Yorks, and Exmouth, Devon, aged 85.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Blackheads

Q.—*A girl of 12 suffers from severe and persistent blackheads on the face. What are the predisposing factors, and how is the condition best treated?*

A.—Blackheads at the age of 12 years are caused by the character and amount of sebum excreted by the sebaceous glands under the influence of hormonal activity. This provokes a hyperkeratosis affecting the whole of the epidermis of the affected parts, but naturally most marked at the orifices.

Presuming that the patient is normal in other respects, local treatment is probably the most important and should consist in regular and frequent washing with soap and hot water, and perhaps the occasional use of a weak solution of a detergent such as 1% cetrimide. The application at night of a paste containing sulphur and resorcin, starting with 2% of each and gradually increasing to 6%, will facilitate the shedding of the blackheads by exfoliation. Exposure to ultra-violet light to produce erythema and peeling is also effective, or small fractional doses of *x*-rays may inhibit the activity of the glands, but such treatment should be prescribed only under expert supervision.

If expression of blackheads is attempted by means of a comedone extractor it should be done with care, otherwise trauma in the region of glands may provoke inflammation or infection.

The taking of vitamin-B complex (on empirical grounds) and small doses of thyroid extract (¼ gr.—16 mg.), and the avoidance of chocolate and cocoa, are sometimes desirable.

Abdominal Testicles and Fertility

Q.—*Is there any treatment for a man of 29 with abdominal testicles who has on two occasions shown azoospermia on examination of the seminal fluid? He was born with undescended testicles, but by puberty they had reached the inguinal canals. An operation at 18 showed that the testicles, although apparently normally developed, had too short vessels for them to be brought into the scrotum. They were therefore returned to the pelvic cavity extraperitoneally. He now wants to have children.*

A.—With exceptions which are so few as to be of no significance, it may be accepted as an axiom that, unless the testes are within the scrotum at the time spermatogenesis should commence, irremediable damage is done to the germinal epithelium, so that placing them within the scrotum at a later date will not lead to spermatogenesis. Even had the length of the cord allowed the testes to be placed within the scrotum at the age of 18, no hope of a successful outcome from that operation could have been entertained. The view which is becoming generally accepted now is that treatment for undescended testicles should begin at an early age, perhaps at 3 to 5 years. If treatment with chorionic gonadotrophin fails to bring about testicular descent, surgical correction of the condition should be considered without undue delay. In any event, the usual effect of gonadotrophin treatment is to cause growth of the spermatic cord, which, should surgery become necessary, makes the operation easier.

One final point: it is quite probable that in many cases the congenital anomaly manifested as cryptorchidism often includes intrinsic testicular defect, so that even after successful correction of the maldescent spermatogenesis may be less than adequate.

Drugs for Hypertension in Pregnancy

Q.—*What place have hypotensive drugs, such as the methonium compounds, in the treatment of hypertension in pregnancy?*

A.—Many substances such as hexamethonium tartrate and bromide and tetraethylammonium chloride and bromide have been tried, and the general experience is that the results are very disappointing. They have a negligible effect on hypertension which is part of eclampsia and pre-eclampsia. In cases of chronic hypertension complicated by pregnancy the fall in blood pressure which results from their intermittent use is very short-lived, and side-effects usually prevent repeated or continued administration. For all practical purposes, therefore, they are of little value in pregnancy hypertension.

Assali and Suyemoto[1] have discussed this subject at some length, and they also report on trials of hydrazinophthalazine and thiophanium compounds. They conclude that a single intravenous injection of 30 to 40 mg. of the former produces a significant fall in blood pressure in true pregnancy toxaemia, and the effect may last as long as 24 hours. It is not, however, very effective in essential hypertension. Thiophanium compounds have a similar but stronger action than tetraethylammonium salts, and in essential hypertension they cause a fall in blood pressure which is sustained for 3 to 10 minutes after a single intravenous injection. A continuous intravenous infusion is necessary to produce a prolonged effect, but there are difficulties in employing this technique. Thiophanium compounds have little effect on hypertension associated with pre-eclampsia and eclampsia, no matter what method of administration is used.

It may be added that the alkaloids of veratrone, previously out of favour, are being used again in certain clinics and encouraging results are recorded, especially in eclampsia and severe pre-eclampsia.

REFERENCE

[1] *Amer. J. Obstet. Gynec.*, 1952, **64**, 1021.

Pica in Pregnancy

Q.—*What accounts for perversion of the appetite during pregnancy? I have a patient who eats coal when pregnant. Is any treatment likely to be effective?*

A.—There is no known anatomical or functional change in the alimentary tract or sense organs to account for bizarre tastes developed by some women during pregnancy. The usual explanations have a psychological basis. It is said, for example, that such women may be found to have shown similar traits at an earlier stage in life and that during pregnancy, and possibly because of some inward conflict or sense of insecurity, they change places with their baby and revert to infantile behaviour. Some authorities invoke a regression to the "oral stage" in development, and a craving for certain articles such as bananas, slate pencils, berries, or caviar is said to reflect ideas of oral impregnation—the particular article representing male or female genitalia. Others, however, point out that perversion of the appetite during pregnancy has been recognized throughout the ages in all parts of the world, and that its origin may lie far back in the ancestry of the mind. It is a common belief amongst primitive peoples that failure to satisfy "longings" results in miscarriage and physical or mental defects in the child. From this it can be argued that the eating of strange articles is blindly purposeful, and that it has as its basis the desire to supply a special need to the foetus or even to give it life. Sometimes an attempt is made to draw an analogy with the habit of a carnivorous animal which occasionally instinctively eats grass or other substance outside the range of its ordinary tastes when it suffers from dietetic deficiency.

These are the sort of views which have been expressed from time to time, and the reader may or may not find them acceptable, or applicable to certain cases. One of the difficulties in accepting them is that a woman some-

times shows perversion of appetite before she has any suspicion that she is pregnant.

There is no specific remedy for pica during pregnancy, nor is any treatment necessary unless the taste is for something which is obviously harmful.

Threadworms and Ammoniated Mercury Ointment

Q.—*In the treatment of threadworms I have applied ammoniated mercury ointment (N.F., 1952) to the perianal region and been dismayed to see threadworms actively wriggling across the anointed area. Is this ointment ovicidal, since it is not vermicidal? Is an alternative vermicidal ointment available?*

A.—The ointment is used for two purposes: in an effort to kill worms as they deposit their eggs on the perianal skin, and to immobilize eggs and prevent their being disseminated into the clothing and elsewhere. The questioner possibly comes to the conclusion that the ointment is not vermicidal on evidence which is too slender, in that it is not stated for how long the worm was observed to live after wriggling across the anointed area. No alternative vermicidal ointment has as yet been shown to be of value.

White Cell Count in Appendicitis

Q.—*What is the value of the white cell count in cases of acute appendicitis? Is it true to say that a rising white count indicates deterioration and that a falling white count shows resolution?*

A.—The white cell count is of limited value in the diagnosis of appendicitis. The experienced surgeon usually places little reliance on this investigation, and the inexperienced is not uncommonly seriously misled by it. In nine out of ten cases a diagnosis of appendicitis can be confidently made by clinical means, and in those cases where there are difficulties in diagnosis they are unlikely to be resolved by the white cell count. To take but one example, acute non-specific mesenteric adenitis is clinically similar to appendicitis and commonly gives rise to a leucocytosis of 15,000 or 20,000 with 80% neutrophils.

A rising white cell count is by no means indicative of deterioration and may be seen in a patient who is forming an abscess and whose general condition is improving. On the other hand, in the patient who starts with a leucocytosis, a falling white cell count usually means resolution.

In conclusion, it should be remembered that many a patient with a gangrenous appendix has a normal or but slightly raised white cell count, and in the aged or the very young the count may be especially misleading.

Chlorbutol and the Nose

Q.—*What is the action of chlorbutol on the nasal mucosa, and its value in the treatment of nasal disease?*

A.—Chlorbutol is a mild sedative and analgesic, and has local analgesic properties. It is also a fungicide. A 1% solution in mineral oil has formed the basis of many popular nasal sprays, though in recent years both chlorbutol and mineral oil have declined in popularity as nasal medicaments. It is used in the nose for its antiseptic, sedative, and analgesic properties; though it is possible that in acute rhinitis the nasal mucosa is further irritated by the volatile preparations, such as menthol and camphor, which are so frequently incorporated with oily solutions of chlorbutol for nasal use.

Deafness from Streptomycin

Q.—*What is the prognosis in the deafness caused by streptomycin therapy? For how long may improvement be expected? Is a hearing-aid useful in these cases?*

A.—Prolonged treatment with streptomycin, particularly if the di-hydro compound is used, may result in deafness. The original calcium compound of streptomycin was found to be vestibulo-toxic, but only in very large doses or over a prolonged period was it cochleo-toxic. In order to avoid this undesirable property the di-hydro compound was developed, but unfortunately this has a selective affinity for the cochlear apparatus. As a rule, it has this effect only if more than 1 gramme daily is given over a period of at least three weeks. Any improvement in hearing following deafness due to streptomycin therapy usually takes place within a few weeks of the withdrawal of the drug. After six months it is most unlikely that any further improvement will occur. The amount of help that can be expected from a hearing-aid will, of course, depend upon the quantity and quality of the hearing which remains. Where the hearing has been seriously affected, there often seems to be some recruitment, which means that the patient will not readily tolerate amplification, and so a hearing-aid may not be of great help. Nevertheless, it should be tried in combination with speech reading, for which special lessons will be needed.

Splenectomy for Leukaemia

Q.—*Is splenectomy ever indicated as a palliative measure in cases of leukaemia? If so, does it have any effect in prolonging life?*

A.—Although splenectomy has been explored for the treatment of leukaemia it has no therapeutic value and does not even serve as a palliative measure. The reason for its trial was probably the extremely satisfactory response in this disease to low-dose splenic radiation. Irradiation of the spleen remains, therefore, the standard treatment for this disease, although various chemotherapeutic agents are now also used, some of equal but certainly of no greater value.

NOTES AND COMMENTS

"Stripping" for Varicose Veins.—Mr. R. ROWDEN FOOTE (London, W.1) writes: In the controversy as to the value of the stripping of varicose veins ("Any Questions?" December 12, 1953, p. 1334), your expert, when criticizing the method, asks, ". . . How often does deep thrombosis actually occur . . . ?" This is something which we are fortunately able to tell him. Among the very numerous reports the following are typical: Linton[1] had one case of deep vein thrombosis in a series of 500 patients. Fenney[2] obtained an 86% excellent result in a series of 150 limbs without complication. In a series of 250 limbs I have had one case of severe deep vein thrombosis, which reacted to anticoagulant therapy with full recovery. The method cannot be blamed in this case, however, since the instructions regarding immediate mobilization of the limb post-operatively had not been carried out. Finally, Warren, of West Roxbury, in a personal letter tells me that he has had one mild case of deep vein thrombosis in a series of 300 limbs, while using a technique in the main similar to my own. A careful technique is all-important, and I have brought out these points in a film of this method which I made in 1952.[3] Sclerosants at the time of operation are more likely to produce deep vein thrombosis than the stripping technique. The performance of local ligations merely spoils the field for the eradication of the varices by stripping.

REFERENCES
1 *Min. Med.*, 1949. **32**, 38.
2 *Ann. Surg.*, 1951, **133**, 386.
3 *Lancet*, 1953, **1**, 858.

Correction.—In our leading article about erythromycin (January 30, p. 261) we mentioned two of its manufacturers—Eli Lilly & Co., Ltd., and Abbott Laboratories Ltd. Upjohn of England Ltd. also market this antibiotic.

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